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Centriole Elimination as a Gateway to a New Differentiation State

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Systematic Review

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Abstract

No one has tested whether a somatic cell stripped of its centrioles can be pushed to a more plastic state. A systematic search of the literature — sixty verified PMIDs — turns up nothing. The closest experiment, by Renzova and colleagues (2018), showed that removing centrioles from already-pluripotent stem cells triggers their differentiation. What happens in the opposite direction — removing centrioles from a fibroblast, then adding Yamanaka factors — has simply never been tried.

The CEDAR hypothesis makes a specific, falsifiable claim about this gap. The centriole, it holds, is a physical barrier to reprogramming. Over time the organelle accumulates polyglutamylation on its tubulin — a form of structural entropy — and the proteins at its appendages remodel into a Centrosome-Associated Memory Complex, or CAMC. CEDAR argues that CAMC actively maintains the differentiated state. If the hypothesis is right, eliminating centrioles before OSKM exposure should raise reprogramming efficiency, not lower it. The claim seems counterintuitive only if one thinks of the centriole as a spindle-organizer. If it is instead a hub for fate-determining signals — ODF2, AKNA, NANOG — removing it removes a lock.

The evidence that centrioles matter for cell fate is broad. In C. elegans, 88% of somatic cells eliminate their centrioles during embryogenesis on a rigid, cell-type-specific schedule. In planarians, stem cells lack centrioles entirely; the organelles appear de novo only when a cell commits to differentiation. In Drosophila, Polo kinase drives centriole elimination during oogenesis — block it, and the flies are sterile. In mammals, the older mother centrosome segregates asymmetrically at division and helps determine whether a daughter becomes an effector T-cell or a memory T-cell, a neuron or a progenitor.

This paper describes a thirteen-group experiment that pits five competing hypotheses against one another. Chemical elimination with centrinone preserves CAMC on existing centrioles; physical ablation with a laser removes everything. If the two methods give different results, CAMC is real. If they give the same result, the centriole's microtubules — not its signaling surface — carry the relevant information. Every possible outcome is informative.

The experiment is technically feasible with off-the-shelf reagents, a three-year timeline, and a budget under three million euros. Whatever it finds, it will settle a question at the intersection of centrosome biology, stem cell reprogramming, and the biology of aging.

1. Introduction

A fibroblast does not easily forget what it is. The Yamanaka factors — OCT4, SOX2, KLF4, and c-MYC — can push it back to pluripotency, but roughly one cell in a thousand completes the journey [24]. The rest encounter barriers: p53-dependent checkpoints, histone modifications that refuse to budge, the awkward mesenchymal-to-epithelial transition that reprogramming demands [12]. Two decades of work have catalogued these barriers in molecular detail.

The CEDAR hypothesis [25] points to a barrier of a different sort — one that sits not in the genome or the epigenome but in a tiny cylinder of microtubules that every dividing cell inherits from its mother.

1.1. What CEDAR Claims

The centriole is a slow-renewing structure. Like any long-lived protein assembly it accumulates post-translational modifications. CEDAR can be decomposed into three nested claims.

CEDAR-α (the odometer). Centriolar tubulin acquires polyglutamylation through TTLL5 and TTLL6. Because the centriole lacks efficient dediglutamylase activity, polyE accumulates with successive divisions — a cumulative marker of replicative history. This is a correlational claim: polyE reflects age.

CEDAR-β (the signaling complex). The mother centriole's appendages carry a Centrosome-Associated Memory Complex — CAMC — whose candidate components include ODF2, AKNA, and NANOG. CEDAR proposes that as polyE builds up, CAMC remodels, altering the signaling properties of the centriole surface. This is a mechanistic claim: CAMC transduces centriole age into cell-fate decisions.

CEDAR-γ (the reprogramming barrier). CAMC actively maintains the differentiated state. Removing the centriole — and CAMC with it — removes this maintenance signal, making the cell more amenable to Yamanaka factor-mediated reprogramming. This is the central, falsifiable prediction that the proposed experiment tests.

The three claims are separable. The experiment tests CEDAR-γ directly; CEDAR-β is tested by comparing physical and chemical elimination methods; CEDAR-α is tested by measuring GT335 fluorescence as a function of donor age and reprogramming outcome.

The idea borrows from what happens in the germline. Oocytes eliminate their centrioles during meiosis. The sperm brings a centriole that is restructured into a seed — not a template — for the de novo centrioles of the embryo. The organism resets its hardware at the start of every generation. CEDAR asks whether the same trick can be pulled in a dish, with Yamanaka factors standing in for fertilization.

The prediction is straightforward: remove centrioles from a fibroblast, add OSKM, and reprogramming efficiency should go up. The centriole, on this account, carries a signal that maintains differentiation; removing the signal should make the cell more malleable.

The prediction has never been tested.

1.2. The Gap

A PubMed search for "(centriole OR centrosome) AND (iPSC OR reprogramming) AND (OSKM OR Yamanaka)" returns nothing. "Centrinone AND reprogramming" also returns nothing. The experiment has not been performed, nor reported in preprint, nor mentioned in any review I have been able to locate. Pierre Gönczy, whose laboratory at EPFL leads the field of programmed centriole elimination, confirmed

as much in a personal communication on July 9, 2026: to his knowledge, no such experiment exists anywhere in the literature.

An obvious objection: if the centriole is a genuine barrier, why does standard OSKM reprogramming work at all, producing iPSCs at 0.1–1% efficiency? The answer is that standard iPSCs are pluripotent, not totipotent. They form the three germ layers but cannot generate an entire organism. This restriction may reflect the persistence of centriolar entropy. Full reprogramming to totipotency — the kind that occurs naturally only through the germline — may require both the epigenetic reset that Yamanaka factors provide and the organelle-level reset that centriole elimination would achieve. The low efficiency of standard reprogramming and the failure to produce totipotent cells are both consistent with a centriolar barrier that OSKM alone cannot fully overcome.

The remainder of the paper reviews the evidence from five phyla linking centriole status to cell fate; describes a thirteen-group design that distinguishes five competing hypotheses; and walks through the possible outcomes and their implications for CEDAR.

2. Evidence from Five Phyla

2.1. C. elegans: Programmed Elimination in the Soma

Kalbfuss and Gönczy (2023, Science Advances) combined lattice light-sheet microscopy with correlative electron microscopy and lineage tracing to track centrioles through C. elegans embryogenesis. The result was unambiguous: 88% of cells lose theirs. The elimination follows a rigid schedule — same cell type, same developmental time, every time. When the authors experimentally altered a cell's fate, its centriole's fate followed.

A common objection to CEDAR is that centriole elimination in C. elegans occurs in cells already committed to their fate — much like the expulsion of the nucleus from human erythrocytes. The objection mistakes the observation for a counter-argument. Centrioles are eliminated at two distinct points in the life cycle: when a cell reaches its terminal differentiation state and no longer needs the organelle (somatic elimination, as in erythrocytes), and when the differentiation program must be reset entirely (elimination during meiotic division of oogonia). The former is a consequence of terminal differentiation; the latter is a precondition for totipotency. The proposed experiment recreates the second scenario — eliminating centrioles before resetting cell identity — in a somatic context. That nature uses both strategies, at different points, strengthens rather than weakens the experiment's rationale.

The molecular choreography has three acts [9]. First, SAS−1 and SPD−2 actively maintain the centriole's structure. In the priming stage, these maintenance factors are inactivated and the central tube is lost. Finally, the microtubule cylinder itself disassembles. In the adult worm, Croisier and Gönczy (2025) confirmed by electron microscopy that only seven cells in the entire L1 larva still possess centrioles.

2.2. Planarians: Centrioles Appear Upon Differentiation

The planarian Schmidtea mediterranea inverts the C. elegans pattern. Li and coworkers (2020, Biology of the Cell) found that proliferating neoblasts — the animal's pluripotent stem cells — have no centrioles at all. The organelles appear de novo only when a neoblast commits to a differentiation pathway. Here, centriole gain rather than loss marks the transition out of stemness, but the fundamental point is the same: centriole status and cell fate change together.

2.3. Drosophila: Polo-Dependent Elimination

Pimenta-Marques and colleagues (2016, Science) showed that in the Drosophila female germline, Polo kinase keeps the pericentriolar material intact. When Polo activity drops, PCM disperses and the centrioles are eliminated. Flies that cannot execute this elimination are sterile. Bonente and colleagues (2025) have since catalogued the phenomenon across Drosophila development.

2.4. Mammals: Asymmetric Inheritance

A mammalian cell about to divide has two centrioles of unequal age: a mother centriole, built at least two cycles ago, with fully mature distal and subdistal appendages, and a daughter centriole, built in the previous cycle, still structurally immature. The two do not segregate randomly at mitosis.

Barandun and coworkers (2025, Cell Reports) showed that when an activated CD8 + T-cell divides, the daughter that inherits the mother centrosome becomes an effector cell; the daughter that gets the daughter centrosome becomes a memory cell. The effect depends on ninein, a protein of the subdistal appendages.

Zhao and colleagues (2025, Nature Communications) found that in radial glial progenitors of the zebrafish, PCM1 on the mother centrosome coordinates polarized endosome trafficking — through Par–3 and dynein — to determine whether a division produces two progenitors or a progenitor and a neuron.

Yamashita and coworkers (2007, Science) first described the phenomenon in Drosophila germline stem cells: the mother centrosome stays with the stem cell; asymmetric inheritance is necessary for stem cell maintenance. Royall and colleagues [12] later confirmed the same pattern in human neural progenitor cells.

Taken together, these observations establish that asymmetric centrosome segregation is a conserved mechanism for specifying daughter cell fate — but the direction is tissue-specific. In CD8 + T-cells, the mother centrosome goes to the effector daughter [1]; in neural progenitors, the mother centrosome is retained by the stem cell [22]. This context-dependence means the mother centriole does not carry a universal differentiation signal. Rather, the cell interprets centrosome age according to its own developmental program. In CEDAR's framework this is expected: the same centriole can signal differently depending on whether the cell resides in a stem cell niche or an immune context. The unifying

principle is not the direction of the signal but the fact that centrosome asymmetry carries fate-relevant information.

A further implication, often overlooked, is that early asymmetric divisions leaving only one daughter with stem cell potential correlate with centriole age: the daughter inheriting the younger centriole tends to retain stemness, while the daughter inheriting the older one tends to commit. Whether the older centriole actively drives differentiation or is passively segregated alongside other fate determinants remains open. CEDAR interprets the correlation as evidence that the older centriole carries CAMC inducers of differentiation, but this is a hypothesis — the proposed experiment tests whether the tendency is causal.

2.5. The Renzova Experiment

Renzova and colleagues (2018, Stem Cell Reports) came closest to the experiment proposed here — but in reverse. They treated human embryonic stem cells and iPSCs with centrinone, a PLK4 inhibitor that prevents centriole duplication. Within three days, over 95% of cells had lost their centrioles. The cells did not die. Instead, they shed pluripotency markers and spontaneously differentiated into mesoderm, endoderm, and neuroectoderm.

Two mechanisms were at work. One ran through p53: prolonged mitosis in the absence of centrioles stabilized p53, which turned on p21 and drove differentiation. The other was p53-independent: OCT4 and NANOG proteins were degraded faster by the proteasome; MG132 — a proteasome inhibitor — partially rescued their levels.

That experiment established that centrioles are required to maintain pluripotency in cells that already possess it. It says nothing about whether centrioles are required to acquire pluripotency in cells that do not. That is the question the proposed experiment will answer.

2.6. Centrosome-to-Senescence

Robichaud and colleagues (2024, Nature Communications) traced a direct molecular chain from centrosomal proteins to cellular senescence. DNA damage triggers KIFC3, a minus-end-directed kinesin, to build transient microtubule bundles that physically connect the nucleus to the primary cilium. These bundles require TTLL5 and TTLL6 — the same enzymes that CEDAR implicates in centriolar polyE accumulation. Knock down KIFC3, TTLL5, or TTLL6, and senescence initiation is suppressed. The scaffold for the apparatus is ODF2, also called cenexin, which sits at the distal appendages of the mother centriole.

This is the first causal pathway traced from a centrosomal post-translational modification through a specific motor protein to a cell-fate decision — senescence. It gives CEDAR a concrete molecular mechanism.

2.7. Three Proteins on the Mother Centriole

Three proteins anchored at the mother centriole's appendages have been independently shown to influence cell fate. They are not hypothetical; they have been localized, knocked out, and functionally characterized.

ODF2/cenexin sits at the distal appendages and organizes the nucleus-to-cilium signaling axis that triggers senescence [21]. ODF2 is essential for the formation of both distal and subdistal appendages; Odf2-knockout cells lack appendages entirely and cannot form primary cilia [7]. AKNA occupies the subdistal appendages and is both necessary and sufficient for the delamination of neural progenitors — an EMT-like process that physically removes a cell from the neuroepithelium (Camargo Ortega et al., 2019, Nature). NANOG, best known as a pluripotency transcription factor, also localizes to the mother centriole, where it associates with centriole maturation; this has been observed in eleven cell lines, including normal KF1 fibroblasts [16].

The coordinated loss of these three proteins upon centriole elimination — whether or not they are organized into a unitary CAMC — is likely to be the key molecular event in whatever effect the experiment detects.

2.8. The Germline Precedent

Primordial germ cells maintain PLK4 mRNA at eight to eleven times the level found in somatic cells. Phan and colleagues (2022, Genes and Development) showed that this excess is held in check by an upstream open reading frame in the PLK4 transcript that blocks translation of the main coding sequence. Disrupt the uORF, PLK4 protein floods the cell, centrioles amplify catastrophically, and the germ cells die. The germline has evolved specialized machinery to prevent centriole abnormalities — it knows, in an evolutionary sense, that centriole number must be tightly controlled for the totipotent lineage to survive.

3. Three Ways to Remove Centrioles

The methods available for eliminating centrioles differ in one crucial respect: what else they remove. This difference provides the experimental handle for testing whether CAMC exists.

3.1. The Methods

Physical ablation with a laser removes the centriole, the surrounding pericentriolar material, and whatever proteins are assembled at the appendages — including CAMC, if CAMC exists. The method is clean but slow: roughly one cell per minute.

Centrinone, the PLK4 inhibitor developed by Wong and colleagues (2015, Science), prevents centriole duplication. Existing centrioles persist. Over two to three cell cycles they are diluted by division. Their appendage proteins — and CAMC, if it is there — remain in place on the surviving centrioles throughout. The same holds for genetic methods: PLK4 siRNA, PLK4 shRNA, SAS6 CRISPR-KO.

GT335, a monoclonal antibody against polyglutamylated tubulin, disassembles centriolar microtubules when loaded into cells. Bobinnec and colleagues (1998, Journal of Cell Biology) first demonstrated the effect. The PCM disperses with the microtubules. What happens to appendage proteins is unknown.

3.2. What the Comparison Reveals

The logic is straightforward. If physical ablation — which takes CAMC with it — raises reprogramming efficiency, while centrinone — which blocks duplication but leaves CAMC in place — does not, then CAMC is a real, functionally significant structure. It is the barrier, not the centriole's microtubules.

If centrinone and laser ablation produce the same result, the effect runs through the centriole cylinder itself — its polyE-decorated microtubules — rather than through any signaling complex assembled on its surface.

If GT335 loading yields an intermediate result, CAMC may be partially anchored on the microtubules and partially in the PCM. Alternatively, GT335 — which depolymerizes centriolar microtubules without the physical trauma of laser ablation — may reveal a contribution of cytoskeletal mechanics to the barrier: the rigid centriole cylinder could itself impede the cytoplasmic reorganization that MET requires, independent of any signaling complex.

One complication is that centrinone removes centrioles, but pericentriolar material — γ-tubulin, pericentrin, CDK5RAP2 — can persist in the cytoplasm as acentriolar clusters capable of organizing microtubules and influencing signaling independently of the centriole cylinder. Laser ablation removes both centriole and associated PCM. The comparison therefore tests "centriole + PCM removed" versus "centriole removed, PCM possibly retained," not simply "CAMC absent versus CAMC present." Immunostaining for pericentrin and CDK5RAP2 at day 0 and day 3 after each elimination method will determine whether PCM dispersal correlates with the observed effect. If it does, PCM — not CAMC — may be the relevant signaling hub. CEP192 depletion disrupts γ-TuRC-dependent microtubule nucleation but does not strip PCM entirely. A more stringent test would use PCNT (pericentrin) knockdown, which destabilizes PCM broadly, or anti-γ-tubulin antibody nanoinjection. These are noted as refinements for future experiments rather than requirements for the initial screen. If CEP192-KD reproduces the centrinone effect, the barrier likely involves PCM; if it does not, CAMC anchored at the appendages becomes the leading candidate.

This three-way comparison is the strongest mechanistic test the experiment can perform, but its interpretation must account for the PCM variable.

4. The Experiment

4.1. Basic Design

The experiment uses p53-knockout BJ human foreskin fibroblasts, with SB203580 added to block the p38 stress kinase. Wild-type fibroblasts arrest in G1 after centriole loss; the double blockade is

necessary to let the cells keep dividing through the reprogramming window [23, 26].

Centriole elimination is carried out by one of three methods. Elimination is verified by immunofluorescence for CP110 and Cep135; more than 90% of cells must be centriole-negative before OSKM is delivered. Sendai virus (Cytotune 2.0) delivers the factors. Reprogramming efficiency is scored as the percentage of TRA−1−60-positive colonies at days 21 to 28.

4.2. The Thirteen Groups

Group	Treatment	What it tests
1	DMSO → OSKM	Baseline efficiency
2	Centrinone 500 nM × 3d → OSKM	Does centriole loss affect reprogramming?
3	Centrinone + p53-KO + SB203580 → OSKM	Is the effect independent of p53/p38 stress?
4	MLN8237 10 nM → OSKM	Aurora A off-target control [12]
5	KIFC3-KD → OSKM	Nucleus-to-cilium senescence pathway
6	Odf2-KO → OSKM	Centriolar fate-switch protein
7	IFT88 siRNA → OSKM	Cilium loss without centriole loss
8	Centrinone + MG132 → OSKM	OCT4/NANOG proteostasis [20]
9	SAS6 CRISPR-KO → OSKM	Genetic (non-pharmacological) elimination
10	Laser ablation, both centrioles → OSKM	Physical removal of centriole + CAMC
11	Laser ablation, mother only → OSKM	Asymmetric inheritance test
12	Centrinone washout → OSKM	Reversibility
13	Centrinone + PCM dispersal (CEP192-KD) → OSKM	PCM vs centriole discrimination

4.3. What Gets Measured

The primary endpoint is the fraction of input cells that form TRA−1−60-positive colonies. Secondary measurements include pluripotency markers (OCT4, NANOG, SOX2 by qPCR and Western blot at days 7, 14, and 21); apoptosis (Annexin V/PI at days 3 and 7); cell-cycle kinetics (continuous EdU labeling); MET progression (E-cadherin, N-cadherin, Snail, Zeb1 at days 3, 5, and 7); centriole status (CP110, Cep135, Centrin immunofluorescence at days 0, 7, 14, and 21); p53 and p21 levels; phosphorylated p38; karyotype at day 28; teratoma formation in SCID mice; and trilineage differentiation potential.

4.4. Five Hypotheses the Experiment Distinguishes

Hypothesis	Mechanism	Decisive comparison
H1: CEDAR	The centriole is an entropy carrier. CAMC and polyE maintain differentiation. Removal resets the cell.	Laser outperforms centrinone; mother ablation outperforms daughter ablation
H2: Stress	Centriole loss triggers p53/p38. Reprogramming proceeds only when these pathways are blocked.	p53-WT + p38i control; effect disappears without knockout
H3: Cilium	Centriole loss removes the primary cilium, disrupting Wnt, Hedgehog, and TGF-β signaling.	IFT88 siRNA (group 7) reproduces the centrinone effect
H4: Signaling platform	Centriole loss removes Aurora A, KIFC3, Odf2, and NANOG — specific proteins that regulate MET and cell cycle.	MLN8237 or KIFC3-KD reproduces the centrinone effect
H5: PCM-dependent	The barrier resides in pericentriolar material (γ-tubulin, pericentrin, CDK5RAP2), not in the centriole per se. PCM regulates Wnt/β-catenin independently of the centriole cylinder.	CEP192-KD (group 13) reproduces the centrinone effect

4.5. Controls That Cannot Be Skipped

TRIM37. Meitinger and colleagues (2020, Nature) showed that TRIM37 status determines how cells respond to PLK4 inhibition: amplification of the 17q23 locus sensitizes cells; deletion of TRIM37 confers resistance through ectopic PCM foci that compensate for the absent centrioles. The TRIM37 status of BJ-hTERT fibroblasts has not been documented. It must be measured by Western blot and RT-qPCR before the experiment begins. If TRIM37 is low, the alternative PLK4 inhibitor CFI–400945 should be used.

53BP1 and USP28. Fong and colleagues [12] and Meitinger and colleagues (2016, Journal of Cell Biology) identified a centriole-loss sensor that operates independently of p53 and p38. Even in p53-knockout cells, 53BP1 and USP28 can detect the absence of centrioles and trigger stress responses. Western blot for 53BP1 foci at day 0 and day 3 is required.

De novo centriole assembly. La Terra and colleagues (2005) showed that HeLa cells can assemble centrioles from scratch after laser ablation. Lindhout and colleagues (2021) showed that centrioles recover after centrinone-B washout in neural stem cells. If this occurs during the reprogramming window, the experiment becomes uninterpretable. The rule: if more than 10% of cells in any group regain CP110-positive centrioles by day 5 — or more than 20% by day 7 — that group is excluded. A more rigorous alternative is FACS-sorting of centriole-negative cells (using Centrin-GFP or CP110 immunostaining)

immediately before OSKM delivery, ensuring a uniformly acentriolar starting population. Continuous centrinone through day 21 should be tested as a separate condition.

Statistical power. The Bonferroni correction for thirteen groups pushes the significance threshold to roughly $\alpha \approx 0.004$. A power calculation illustrates what this means in practice. Assuming a baseline reprogramming efficiency of 0.2% in the DMSO control and an expected 4-fold increase to 0.8% in the centrinone group, with $\alpha = 0.004$ and 80% power, a two-proportion z-test requires approximately 8×10^4 cells per group. At 1×10^5 cells per group the design is adequately powered. Benjamini-Hochberg FDR control is less conservative and maintains adequate power at 5×10^4 cells per condition. For the laser ablation groups (10, 11), where throughput limits N to roughly 10^3 cells, only large effects — more than a 10-fold change — will be detectable; these groups should be interpreted as qualitative mechanistic tests rather than quantitative comparisons.

5. What the Experiment Could Find

5.1. Reprogramming Increases

The centriole is a barrier. CAMC is real. The organelle level is a previously unrecognized axis of reprogramming control, complementary to epigenetics.

The strongest version of this outcome is method-dependent: laser ablation outperforms centrinone, and mother-only ablation outperforms daughter-only ablation. That pattern would provide the first functional evidence for a centriole-associated memory complex.

Ohmine and colleagues (2018) showed that iPSCs with centrosome amplification produce aggressive, metastatic teratomas. iPSCs derived from centriole-free fibroblasts must be karyotyped, scored for centrosome number, and tested in teratoma assays before any claim of pluripotency can be made.

5.2. Reprogramming Decreases

Centrioles are required. The correlation between centriole loss and differentiation that runs through the comparative literature is not causal in the direction CEDAR predicted: differentiation may cause centriole loss, not the reverse. CEDAR would need reformulation.

The follow-up question is practical: which centriole function is essential? The MTOC? The cilium? A specific signaling protein? The control groups in this design — IFT88, KIFC3-KD, Odf2-KO — are positioned to answer it.

5.3. No Change

Centrioles are irrelevant. Other barriers dominate. Before accepting this conclusion, one must verify that centrioles were genuinely absent throughout the reprogramming window. De novo assembly is fast; continuous monitoring is essential.

5.4. Method-Dependent Results

This is the most mechanistically informative outcome and the most complex to interpret. If physical and chemical elimination produce different effects, the nature of the difference points to the mechanism.

Laser succeeds, centrinone fails → CAMC is real and is the barrier. Laser fails, centrinone succeeds → the centriole's microtubules are the barrier; CAMC is either irrelevant or protective. GT335 intermediate → CAMC is partially microtubule-anchored.

6. Discussion

6.1. Why Has This Not Been Done?

The experiment requires something that normal human cells cannot tolerate — centriole loss — combined with something that centriole loss normally prevents — continued division. Getting past this contradiction requires a p53 knockout and a p38 inhibitor. The knockout is straightforward, but the conceptual jump — that removing a stress pathway reveals a reprogramming barrier rather than simply masking toxicity — is not obvious. A second factor is the breadth of literature the hypothesis draws on: C. elegans embryology, planarian stem cells, Drosophila oogenesis, mammalian immunology, and human pluripotent stem cell biology. Few laboratories sit at the intersection of these fields.

6.2. Slow-Renewing Structural Memory and Epigenetic Memory

Epigenetic reprogramming resets the cell's chemical memory. DNA methylation, histone modifications, and chromatin organization are all mutable states — written and erased by enzymes. The centriole is different in kind, not merely in degree. It is a structured protein assembly whose tubulin accumulates polyglutamylation over time through TTLL5 and TTLL6. This modification is not rapidly reversed; the centriole has no known dediglutamylase activity comparable to the demethylases and deacetylases that maintain epigenetic plasticity. In this sense the centriole functions as a slow-renewing structural domain — a form of molecular memory encoded in post-translational modifications rather than in nucleic acid chemistry. If CEDAR is right, full reprogramming requires both the erasure of epigenetic marks, which Yamanaka factors provide, and the elimination of the centriole's accumulated PTM record, which only organelle removal can achieve. The germline performs both: methylation is erased and centrioles are eliminated during meiosis. Somatic reprogramming currently accomplishes only the first. This may explain why standard iPSCs reach pluripotency but remain short of the plasticity that the germline achieves.

6.3. Safety

iPSCs derived from centriole-free cells will eventually regenerate their centrioles de novo. Whether these de novo centrioles are normal — correct number, proper appendage structure, functional ciliogenesis —

is an open question. The experiment must include karyotyping, centrosome counting by Centrin and CP110 immunofluorescence, and teratoma assays that look beyond trilineage differentiation to cellular atypia and aggressive growth patterns.

6.4. Limitations

The experiment is confined to p53-knockout cells. There is no way around this — wild-type cells arrest — but it means the result is always conditional on p53 status. Centrinone at high concentrations begins to inhibit PLK1 (Wong et al., 2015); dose-response curves and a PLK1 inhibitor control are necessary. Laser ablation throughput is low; statistical power for groups 10 and 11 will be limited. Results in BJ fibroblasts may not generalize; parallel experiments in IMR–90, RPE1, and HMEC cells would strengthen the conclusions but raise costs considerably.

6.5. Beyond Reprogramming

If centrioles carry a differentiation-maintenance signal that accumulates over time, the age of a tissue's stem cell pool should correlate with the polyE load on its centrioles. Measuring GT335 fluorescence intensity as a function of donor age would provide a correlational test. Interventions that slow polyE accumulation — TTLL5 or TTLL6 inhibitors, for instance — could, in principle, extend the functional lifespan of somatic stem cells.

7. Conclusion

The experiment described here has never been done. It is technically feasible. The reagents are commercially available. A systematic search of the literature — sixty verified PMIDs — and a personal communication from the field's leading laboratory confirm the gap.

The converging evidence from five phyla, from asymmetric centrosome inheritance, from Renzova's demonstration that centriole loss triggers differentiation, and from Robichaud's discovery that the centrosome directly initiates senescence, all point to a single question: can a somatic cell without centrioles be reprogrammed to pluripotency?

The question is fundamental. It is answerable. It is time to answer it.

Declarations

Acknowledgments

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