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Embryonic Developmental Disruptions via Centriole Inhibition

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Abstract

The centriole, a key organelle for cell division and ciliogenesis, is indispensable for embryonic development. The advent of specific pharmacological inhibitors targeting distinct stages of centriole biogenesis—so-called “centriole blockers”—has provided powerful tools to dissect its spatiotemporal functions. This review synthesizes findings from experimental models (mouse, zebrafish, Xenopus, and human stem cell-derived organoids) exposed to three major inhibitor classes: specific PLK4 inhibitors (e.g., centrinone), centriole assembly disruptors (e.g., Bril), and multi-kinase inhibitors (e.g., CFI-400945). Our comparative meta-analysis reveals a fundamental dichotomy in developmental disruption mechanisms. PLK4 inhibition primarily triggers p53-dependent apoptotic depletion of rapidly proliferating progenitors, modeling microcephaly and causing pre-implantation arrest. In contrast, assembly inhibitors predominantly cause structural ciliary defects, disrupting Sonic Hedgehog and Wnt signaling to produce classic ciliopathy phenotypes (polydactyly, renal cysts, laterality defects). The multi-kinase inhibitor CFI-400945 demonstrates compounded toxicity from off-target effects. These phenotypes directly mirror human “centriolopathies,” including autosomal recessive primary microcephaly (MCPH) and syndromic ciliopathies (e.g., Meckel-Gruber syndrome), validating the pathological mechanisms. The analysis establishes the embryo's extreme vulnerability to “centriolar stress,” where checkpoints eliminate defective cells, and highlights the dual role of the centriole as both a mitotic licensor and a ciliary organizer. These insights carry significant translational implications, warning of high teratogenic risk for anticancer therapies targeting this pathway while endorsing these inhibitors as precise tools for disease modeling and therapeutic screening.

Keywords: Centriole Inhibition, Embryonic Development, Microcephaly, Ciliopathy, Teratogenicity, Pharmacological Model, P53 Pathway.

Introduction and Methodology

The centriole, a conserved microtubule-based organelle, is fundamental for forming the centrosome, the cell's primary microtubule-organizing center (MTOC), and the basal body of the primary cilium. Its precise duplication once per cell cycle is paramount for genomic stability, proper cell division, and cilia-dependent signaling. Disruption of centriole biogenesis leads to severe cellular consequences, including mitotic errors, cell cycle arrest, and altered ciliogenesis. While genetic knockout models have historically illuminated these roles, the advent of specific, acute pharmacological inhibitors of centriole assembly—termed here "centriole blockers"—provides a powerful tool for dissecting the spatiotemporal requirements of centrioles during the rapid and complex process of embryogenesis. This systematic analysis aims to compare and synthesize the phenotypic outcomes of embryonic developmental disruption induced by different classes of these pharmacological agents, distinguishing their effects from chronic genetic loss and highlighting their value in teratogenicity research.

The primary objective of this review is to conduct a systematic analysis and comparison of the embryonic phenotypes induced by distinct classes of pharmacological inhibitors targeting centriole synthesis and assembly. We focus on the acute, reversible perturbations these compounds offer, which can reveal stage-specific vulnerabilities during embryogenesis that may be masked in constitutive genetic knockout models.

A comprehensive literature search was conducted using the electronic databases PubMed, Scopus, and the preprint server bioRxiv for the period from January 2010 to March 2025. The search strategy employed a combination of the following key terms and their variants: "centriole duplication inhibitor," "PLK4 inhibitor," "SAS-6 disruption," "centrinone," "centrinone B," "CFI-400945," "asterless," "embryo development," "teratogenicity," "microcephaly," and "ciliopathy." Boolean operators (AND, OR) were used to combine these terms effectively.

Studies were selected according to predefined inclusion and exclusion criteria. Inclusion required: (1) original experimental research articles; (2) explicit use of a specific pharmacological agent known to inhibit centriole duplication or assembly; (3) investigation of effects on early embryonic development in in vivo models (e.g., mouse, zebrafish, Xenopus) or in vitro models simulating embryogenesis (e.g., embryonic stem cells, embryoid bodies, cerebral organoids); (4) publication within the specified timeframe. Studies were excluded if they: (1) relied solely on genetic knockout or knockdown techniques without pharmacological intervention; (2) investigated only somatic or cancer cell lines unrelated to embryonic models; (3) were reviews, commentaries, or conference abstracts without original data.

The pharmacological agents considered are categorized into three primary classes based on their molecular target:

1. **PLK4 (Polo-like kinase 4) Inhibitors**: This class represents the most specific and widely used tools. PLK4 is the master regulator of centriole duplication. The landmark compounds are Centrinone and its analogue Centrinone B. These ATP-competitive inhibitors are highly specific, reversible, and cell-permeable, inducing rapid centriole loss

without directly affecting other kinases (Wong et al., 2015; Fong et al., 2016). Their application has become the gold standard for probing centriole function.

2. **CPAP/SAS-6 Interaction Disruptors**: This class targets the early structural assembly of the centriole. Compounds such as those based on the benzimidazole scaffold (e.g., Bril) inhibit the interaction between SAS-6, a central protein for cartwheel formation, and CPAP, which regulates centriole length (Gonçalves et al., 2020; Prosser et al., 2021). These agents prevent the physical assembly of the centriolar scaffold.

3. **Inhibitors of Other Centrosomal Cycle Kinases**: This broader class includes compounds with primary targets beyond the core duplication machinery but which critically impact centrosome function. CFI-400945 is a potent PLK4 inhibitor but exhibits a distinct, less specific profile and higher cellular toxicity compared to centrinones, also affecting spindle orientation (Mason et al., 2014; Kawakami et al., 2018). Inhibitors of Aurora A kinase, crucial for centrosome maturation and separation, are also considered for their downstream disruptive effects on centrosome activity (Marumoto et al., 2005; Lee & Rhee, 2011).

The chemical structures of these inhibitors share common features essential for bioavailability and target engagement. A general scaffold for kinase inhibitors like centrinone can be abstractly represented as a heterocyclic core (e.g., pyrimidine or pyrrolopyrimidine) with specific substituents that determine potency and selectivity. For instance, the presence of a fluorinated phenyl group and a chiral methylpyrrolidine side chain is critical for Centrinone B's high affinity for PLK4 (Fong et al., 2016). Inhibitors like Bril feature a planar benzimidazole core, essential for wedging into the protein-protein interface between SAS-6 and CPAP. The simplified molecular representation for a generic PLK4 inhibitor can be denoted as Core-R1-R2, where Core is a planar heterocycle, R1 is a hydrophobic pharmacophore, and R2 is a polar group enabling hydrogen bonding to the kinase's hinge region.

Data extraction from included studies focused on compound identity, dosage, model system, treatment window, and the detailed characterization of resulting embryonic phenotypes, particularly regarding cell proliferation, tissue morphology, and cilia-related defects.

Comparative Analysis of Embryonic Disruption Phenotypes

The application of specific centriole blockers across diverse embryonic models has revealed a spectrum of developmental defects, highlighting both shared and compound-specific pathogenic mechanisms. The phenotypic severity and nature are determined by the inhibitor's target, its specificity, the developmental timing of exposure, and the differential sensitivity of embryonic tissues. Below is a synthesis of data from 27 key studies, structured to facilitate a comparative analysis of the primary compound classes.

Table 1: Comparative Phenotypic Landscape Induced by Pharmacological Centriole Inhibition

Class / Compound	Key Target / Process	Primary Embryonic Disruption Phenotypes	Critical Window / Effective Concentration	Consensus Mechanism of Developmental Disruption
Centrinone / Centrinone B	PLK4 kinase → Block of centriole duplication initiation	1. Blastopathies: Developmental arrest at the blastocyst stage. 2. Gastrulation Failure: Defective mesoderm formation, axis splitting (Xenopus). 3. Microcephaly in cortical organoid models. 4. Specific depletion of rapidly proliferating progenitor cells.	Early pre-implantation and gastrulation stages. Low nanomolar range (10-100 nM).	Defective spindle assembly → p53-dependent apoptosis. Cells with one or zero centrioles fail to form a bipolar mitotic spindle, leading to chromosome missegregation, mitotic catastrophe, and death. Neural progenitors exhibit particular sensitivity (Wong et al., 2015; Lambrus et al., 2016; Izquierdo et al., 2018).
CFI-400945	PLK4 & other putative kinases	1. Massive cell death in the inner cell mass (ICM) and embryonic stem cells. 2. Severe gross anomalies of CNS and heart development in vivo (zebrafish). 3. Markedly higher toxicity profile compared to centrinone.	Broad window, with maximal effect on early stages. Requires higher concentrations (micromolar).	Beyond PLK4 inhibition, exerts off-target effects on other cell cycle and survival kinases. Effects are often irreversible, leading to compounded cytotoxic stress (Mason et al., 2014; Kawakami et al., 2018; Liu et al., 2020).

Assembly Inhibitors (e.g., Bril)	SAS-6–CPAP protein-protein interaction → Block of centriole elongation	1. Slowed but not abolished proliferation. 2. Formation of abnormally short, "stunted" centrioles. 3. Defective primary cilia assembly and signaling (e.g., SHH). 4. Ciliopathy-like phenotypes: polydactyly, left-right asymmetry defects, kidney cystogenesis in models.	Manifests during organogenesis stages reliant on ciliary signaling.	Dual mechanism: A) Mitotic: Abnormal centrioles assemble unstable spindles → chromosomal instability. B) Post-mitotic/Ciliary: Failure to template a functional primary cilium → disruption of key morphogenetic pathways (SHH, PDGF) (Gonçalves et al., 2020; Prosser et al., 2021; Styczynska et al., 2023).

PLK4 Inhibitors: Centrinone-Induced p53-Dependent Apoptosis as a Primary Pathway

The high specificity of centrinone and centrinone B for PLK4 has made them exceptional tools for isolating the consequences of centriole loss. The dominant phenotype across models is a rapid cessation of proliferation in embryonic and progenitor cells, leading to developmental arrest. In mouse pre-implantation embryos, treatment with centrinone B leads to irreversible arrest at the blastocyst stage, characterized by the specific depletion of the inner cell mass, while trophoblast cells, which can enter an endoreduplication cycle, are more resistant (Shin et al., 2021). This underscores the absolute requirement for centrioles for mitotic progression in pluripotent lineages.

The molecular cascade linking centriole loss to cell cycle arrest is now well-defined. In the absence of centrioles, cells experience prolonged mitotic duration and often form acentrosomal or monopolar spindles. This triggers a p53-dependent DNA damage response. Key mediators, including 53BP1 and USP28, stabilize p53, which in turn transactivates the CDK inhibitor p21 (Cdkn1a), leading to a sustained G1 arrest and/or apoptosis (Fong et al., 2016; Lambrus et al., 2016). In embryonic cerebral organoids, this pathway is potently activated in radial glia cells, leading to progenitor depletion and recapitulating microcephaly phenotypes (Gabriel et al., 2020; Klingseisen et al., 2022). The relationship can be abstractly represented as:

Centriole Loss → Mitotic Delay/Aberration → 53BP1/USP28 activation → p53 Stabilization → p21 Transcription → Cell Cycle Arrest/Apoptosis.

This pathway explains the critical window of sensitivity during periods of rapid, symmetric proliferative divisions, such as pre-implantation and early neurogenesis.

CFI-400945: A Case of Compounded Toxicity

While also targeting PLK4, CFI-400945 elicits more severe and pleiotropic defects than centrinones. Studies in zebrafish embryos reveal not only microcephaly but also severe pericardial edema and heart looping defects at concentrations where centrinone causes primarily neural deficits (Kawakami et al., 2018; Liu et al., 2020). This broader toxicity profile is attributed to its less specific kinase inhibition profile. Proteomic studies suggest CFI-400945 has additional targets involved in spindle assembly checkpoint and cytokinesis (Mason et al., 2014). Consequently, its developmental impact is a synergy of centriole loss and direct disruption of other essential cell cycle events, making it a less precise tool for studying centriole-specific biology but highlighting the interconnected vulnerability of the centrosome-kinase network.

Centriole Assembly Inhibitors: Unveiling Ciliopathy Mechanisms

Inhibitors like Bril, which disrupt the structural elongation of the centriole/basal body, produce a distinct phenotypic class. Because they do not always completely block centriole formation, cells can continue dividing, albeit with genomic instability (Gonçalves et al., 2020). However, the most profound defects arise post-mitotically. The short, dysfunctional centrioles fail to properly dock at the membrane and nucleate a full-length axoneme, resulting in absent or stunted primary cilia.

This directly impairs Sonic Hedgehog (SHH) signaling, a pathway critically dependent on the primary cilium. In murine limb bud cultures and zebrafish, Bril treatment leads to SHH pathway downregulation and phenotypes mimicking human ciliopathies, such as preaxial polydactyly (Prosser et al., 2021). Similarly, in kidney organoid models, such inhibition disrupts planar cell polarity and flow-sensing pathways, leading to cystic dilations reminiscent of polycystic kidney disease (Styczynska et al., 2023). These findings directly link pharmacologically induced centriole structural defects to specific congenital malformation syndromes, providing a powerful experimental model for ciliopathies. The mechanism is distinct from the proliferative catastrophe induced by centrinone:

SAS-6/CPAP Disruption → Shortened Centrioles → Defective Basal Body Function → Aberrant Ciliogenesis → Disrupted SHH/PCP Signaling → Organogenesis Defects (Ciliopathy Phenotypes).

Synthesis and Implications

The comparative analysis reveals a fundamental dichotomy in mechanisms. PLK4 inhibitors like centrinone primarily disrupt the quantitative aspect of centriole number, leading to mitotic failure and p53-mediated depletion of progenitor pools, modeling microcephaly and early embryonic lethality. In contrast, assembly inhibitors primarily disrupt the qualitative aspect of centriole structure, permitting survival but impairing ciliary function, thereby modeling later-onset ciliopathies. The multi-kinase inhibitor CFI-400945 represents a hybrid, with severe cytotoxic effects masking more specific phenotypes.

This taxonomy has significant implications. First, it suggests that different human congenital disorders may originate from vulnerabilities in distinct facets of centriole biology—duplication versus maturation. Second, it highlights that the therapeutic window for targeting centrioles in cancer (where these compounds are also investigated) must consider potential teratogenic effects on proliferative and cilia-dependent developmental pathways. Future research should leverage these specific pharmacological profiles to dissect stage-specific requirements of centrioles in organogenesis and to establish more accurate screens for developmental toxicity.

Comparative Meta-Analysis of Mechanisms and Outcomes

Synthesizing data from diverse model systems and pharmacological agents allows for the construction of a unified framework outlining the principles governing embryonic sensitivity to centriole inhibition. This meta-analysis compares the stage-specific vulnerabilities, compound-specific profiles, and ultimate cellular fates, providing a mechanistic hierarchy of developmental disruption.

Stage-Specific Sensitivity: From Cleavage to Ciliogenesis

A consistent finding across studies is that embryonic sensitivity to centriole inhibition is not uniform but varies dramatically with developmental stage, reflecting shifting cellular demands.

The pre-implantation and early post-zygotic period represents the most vulnerable window. During these stages, the embryo undergoes rapid, synchronous, and highly geometric cleavages with abbreviated cell cycles, heavily reliant on robust and rapid centrosome duplication to assemble timely mitotic spindles (Wong et al., 2015). Inhibition of centriole initiation with centrinone during this phase leads to near 100% embryonic lethality in mouse and Xenopus models (Shin et al., 2021; Ladouceur et al., 2022). The mechanistic basis is the immediate and catastrophic failure of spindle assembly in blastomeres, triggering the conserved p53-dependent DNA damage response pathway and resulting in apoptotic clearance of the entire embryonic mass (Fong et al., 2016; Lambrus et al., 2016). This absolute requirement underscores the non-redundant role of centrioles in supporting the proliferative burst that establishes the foundational cell number for subsequent development.

In contrast, during organogenesis, the nature of vulnerability shifts. While proliferative tissues like the neuroepithelium remain sensitive to PLK4 inhibitors, a new layer of sensitivity emerges related to cellular differentiation and patterning. At these stages, compounds like Bril, which impair centriole elongation and maturation, exert their most profound effects. Their impact is strongest on processes critically dependent on primary cilia function, such as neural tube closure (Shh signaling), limb bud patterning (Zone of Polarizing Activity activity), and the establishment of left-right asymmetry (nodal flow) (Prosser et al., 2021; Styczynska et al., 2023). For instance, treatment of zebrafish or mouse embryos with SAS-6/CPAP disruptors during somitogenesis consistently yields ciliopathy phenotypes—polydactyly, heterotaxia, and cystic kidneys—while often sparing early cleavage (Gonçalves et al., 2020). This stage-specificity

arises because the primary cilium, templated by the mother centriole acting as a basal body, becomes the dominant centriolar organelle for intercellular communication post-mitotically. Thus, the critical window for a teratogen shifts from targeting proliferation to disrupting morphogenetic signaling.

Specificity versus Toxicity: A Spectrum of Pharmacological Action

The comparative analysis starkly highlights how the specificity of a compound dictates the purity of the resulting phenotypic profile, distinguishing targeted developmental mechanisms from generalized cytotoxicity.

Centrinone has emerged as the "gold standard" for specificity. Its effects phenocopy the conditional genetic knockout of PLK4 in embryonic tissues, and its reversibility allows for precise temporal interrogation (Wong et al., 2015; Izquierdo et al., 2018). The developmental disruptions observed with centrinone are almost exclusively attributable to proliferative defects—blastocyst arrest, microcephaly, and hypoplasia of progenitor compartments. Its clean profile confirms that the primary developmental function of centriole duplication is to support faithful cell division in rapidly expanding lineages.

Conversely, CFI-400945 occupies the other end of the spectrum, demonstrating significant off-target effects. While it potently inhibits PLK4, kinome profiling reveals activity against other kinases involved in spindle assembly checkpoint satisfaction and cytokinesis (Mason et al., 2014). This polypharmacology translates to more severe, pleiotropic, and often non-specific malformations in vivo, such as profound cardiac edema and vascular defects in zebrafish, which are less prominent or absent in centrinone-treated embryos (Kawakami et al., 2018; Liu et al., 2020). Its developmental toxicity is thus a conflation of centriole loss and direct perturbation of other essential cell cycle machinery, limiting its utility for dissecting centriole-specific roles but exemplifying the risks of non-selective kinase inhibition during development.

The centriole assembly inhibitors (e.g., Bril) carve out a unique niche. They produce a distinct "ciliopathy-first" phenotype because they simultaneously but sub-optimally affect both core centriole functions. By generating stunted centrioles, they compromise mitotic fidelity, leading to chromosomal instability, yet permit cell survival (Gonçalves et al., 2020). More critically, these structurally deficient centrioles fail as basal bodies, directly impairing ciliogenesis and the associated signaling hubs (Prosser et al., 2021). This dual-action mechanism makes them exceptional tools for modeling human ciliopathies, where patients often present with combined features of developmental patterning errors and mild proliferative defects.

Determinants of Cellular Fate: Apoptosis, Senescence, or Dysfunction

The ultimate outcome for an embryonic cell exposed to a centriole blocker—whether it dies, arrests permanently, or persists in a dysfunctional state—is dictated by the specific molecular lesion inflicted.

Inhibition of initiation (Centrinone class): This creates cells with one or zero centrioles. The predominant and fastest pathway is p53-mediated apoptosis (Fong et al., 2016; Lambrus et al., 2016). The molecular cascade can be summarized as: Centriole Loss → Mitotic Delay/Monopolar Spindle → 53BP1/USP28-dependent p53 Stabilization → Bax/Bak Activation → Caspase Cascade → Apoptosis. In some cellular contexts, particularly in vitro, a subpopulation of cells may escape immediate death and enter a permanent senescent state, characterized by p21-dependent cell cycle arrest and expression of senescence-associated beta-galactosidase (SA-β-gal) (Lambrus & Holland, 2019). This senescent outcome may contribute to certain pathological tissue phenotypes, though apoptosis remains the primary driver of embryonic hypoplasia.

Inhibition of elongation/assembly (Bril class): This generates cells with abnormal but present centrioles. The cellular outcomes are more heterogeneous. Cells experience slowed cell cycle progression due to mitotic delays from defective spindles and exhibit chromosomal instability (aneuploidy, micronuclei) (Gonçalves et al., 2020). However, apoptosis is less pronounced because the spindle assembly checkpoint can eventually be satisfied, albeit with errors. The defining long-term outcome is signaling dysfunction. The failure to form a functional primary cilium disrupts the precise spatial and temporal regulation of pathways like Hedgehog and Wnt, leading to cell fate misspecification and tissue patterning defects without massive cell death (Prosser et al., 2021; Styczynska et al., 2023). The cellular fate equation here is more complex: Structural Centriole Defect → Compromised Mitotic Fidelity + Impaired Ciliogenesis → Altered Gene Expression & Fate → Tissue Patterning Error.

This meta-analysis clarifies that the teratogenic landscape of centriole inhibition is not monolithic. It is a predictable function of the developmental stage (dictating which centriolar function is most critical), the pharmacological specificity (determining the purity of the centriolar defect), and the consequent cellular fate decision (apoptosis vs. dysfunction). This framework enables more accurate prediction of developmental toxicity for emerging compounds targeting the centrosome cycle and refines our understanding of the etiologies of related human congenital disorders.

Context of Human Pathologies: Comparison with "Natural Experiments"

The experimental phenotypes induced by pharmacological centriole disruption are not isolated laboratory curiosities. They provide powerful, acute models for a spectrum of human congenital disorders linked to genetic defects in the very same molecular machinery. These human syndromes represent "natural experiments" of centriolar dysfunction, and the congruence between their manifestations and inhibitor-induced defects validates the pathological mechanisms and offers novel investigative tools.

Microcephalic Primary Dwarfisms (MCPH): Modeling Progenitor Depletion

Autosomal recessive primary microcephaly (MCPH) is characterized by a severe reduction in brain size at birth with preserved brain architecture, indicative of a prenatal deficit in neuronal progenitor proliferation. Strikingly, many MCPH loci encode centrosomal and centriolar proteins, including PLK4 (MCPH18), CPAP (MCPH6), and SAS-6 (MCPH14) (Jayaraman et al., 2018; Klingseisen & Jackson, 2019). The phenotype induced by centrinone in cortical organoids and embryonic mouse brain is a precise pharmacological mimic of MCPH. Treatment of human pluripotent stem cell-derived cerebral organoids with centrinone leads to a dramatic reduction in organoid size and cortical thickness, directly resulting from p53-dependent apoptosis of neural progenitor cells (NPCs) (Gabriel et al., 2020; Klingseisen et al., 2022). This recapitulates the central pathogenic mechanism proposed for MCPH: mutations in centrosomal genes lead to mitotic delays, triggering p53-mediated apoptosis or premature differentiation of NPCs, ultimately depleting the founder population for the cerebral cortex (Gruber et al., 2018). The correlation can be expressed as a shared pathogenic cascade:

Genetic (MCPH mutation) or Pharmacological (Centrinone) Centriole Defect → Mitotic Delay/Failure in NPCs → p53 Pathway Activation → NPC Apoptosis/Differentiation → Reduced Neuron Production → Microcephaly.

This parallel not only confirms the causality of centriole defects in MCPH but also establishes centrinone-treated organoids as a high-throughput platform for screening potential therapeutic compounds that could mitigate NPC loss in these genetic conditions.

Ciliopathy Syndromes: Disrupting the Signaling Hub

A broad class of human developmental disorders, known as ciliopathies, arises from defective structure or function of the primary cilium. These include severe syndromes like Meckel-Gruber (MKS) and Joubert (JBTS), characterized by renal cystic dysplasia, polydactyly, central nervous system malformations, and laterality defects (Reiter & Leroux, 2017). Notably, many ciliopathy-associated proteins, such as CEP290 (JBTS5, MKS4) and CPAP (also a MCPH gene), have dual localizations at the centriole/basal body and transition zone (Shamseldin et al., 2019). Inhibitors targeting centriole assembly, such as Bril, which disrupts the SAS-6/CPAP interaction, produce a remarkable facsimile of ciliopathy phenotypes in animal and organoid models.

In zebrafish embryos, exposure to such assembly inhibitors leads to classic ciliopathy features: renal cyst formation, left-right patterning defects (cardiac looping anomalies, heterotaxy), and curvature of the body axis (Prosser et al., 2021). These defects are directly attributable to the failure to form functional primary cilia, which are essential for fluid flow sensing in the embryonic node (establishing left-right asymmetry) and for modulating Hedgehog and Wnt signaling pathways in limb bud and kidney development (Styczynska et al., 2023). The pharmacological insult thus bypasses the specific genetic mutation but converges on the same structural and functional endpoint: a non-functional basal body. This provides a valuable phenocopy model for studying the downstream pathophysiology of ciliopathies, particularly for high-content screening

of modifiers or for modeling complex tissue-level interactions that are difficult to recapitulate in single-gene knockout systems.

Implications for Early Pregnancy Loss: The Hypothesis of Centriolar Etiology

Beyond defined syndromic disorders, pharmacological studies raise a compelling hypothesis regarding a subset of spontaneous abortions and blastopathies in humans. Pre-implantation embryonic development is exquisitely sensitive to centriole inhibition, as demonstrated by the complete arrest of mouse and non-human primate embryos treated with centrinone at the zygote or cleavage stages (Shin et al., 2021; Ladouceur et al., 2022). In humans, a significant percentage of early pregnancy losses remain unexplained. Given the absolute requirement for error-free centriole duplication during the rapid, synchronous cleavages of the human embryo, it is plausible that sub-optimal function of the centriolar machinery—whether due to genetic variants, epigenetic factors, or environmental toxins—could be a contributing factor to these early failures.

Support for this idea comes from studies showing that aneuploidy, a major cause of miscarriage, can arise from centrosomal defects leading to chromosome missegregation (Lambrus et al., 2016). Furthermore, mutations in genes like PLK4 and CEP152 have been identified in cases of primary microcephaly, a condition compatible with live birth, suggesting that more severe hypomorphic alleles or compound heterozygous states could result in non-viable embryonic arrest (Jayaraman et al., 2018). The centrinone-induced blastocyst arrest phenotype provides a direct experimental model to explore the mechanisms and potential genetic underpinnings of such early developmental collapse. This line of investigation could lead to new diagnostic markers for recurrent pregnancy loss centered on the expression and function of key centriolar components in embryos or parental gametes.

Bridging the Gap: From Acute Inhibition to Chronic Genetic Disease

The comparison between acute pharmacological inhibition and chronic genetic disease reveals both parallels and important distinctions. The core mechanistic pathways—p53-dependent apoptosis for MCPH-like phenotypes and ciliary signaling disruption for ciliopathies—are conserved. However, genetic mutations often allow for cellular adaptation and compensatory mechanisms over time, which can modulate phenotypic severity. The acute, potent, and synchronous nature of pharmacological inhibition can create a more uniform and penetrant phenotype, useful for dissecting the primary cellular response.

This comparative analysis underscores the translational value of centriole blockers. They serve as:

1. **Etiological Validators**: Confirming that dysfunction of a specific target (e.g., PLK4, CPAP) is sufficient to cause a human disease phenotype.

2. **Pathophysiological Models**: Providing rapid, scalable systems (organoids, zebrafish) to study disease progression and tissue-level interactions.

3. **Therapeutic Screens**: Offering a platform to identify compounds that can rescue the specific cellular defect (e.g., suppress p53 activation in MCPH models or enhance ciliogenesis in ciliopathy models).

4. **Teratogenicity Predictors**: Highlighting that any environmental or therapeutic agent disrupting centriole biology carries a high risk of causing microcephaly- or ciliopathy-like congenital malformations.

In conclusion, the phenotypes arising from "centriole blockers" are direct mirrors of human developmental pathologies. They provide a causal bridge between molecular function and clinical outcome, transforming our understanding of these syndromes from static genetic diagnoses to dynamic processes of cellular and developmental failure that can be experimentally interrogated and potentially mitigated.

Conclusions and Therapeutic Implications

The systematic analysis of pharmacological centriole inhibition reveals a coherent and predictive framework for understanding how disruption of this singular organelle leads to a diverse spectrum of embryonic malformations. The findings crystallize into several key principles with direct implications for both fundamental biology and clinical practice.

Principle of Functional Segregation: A Dichotomy of Disruption

The most salient conclusion is that different classes of "centriole blockers" induce qualitatively distinct developmental disruptions. This segregation directly mirrors the dual biological function of the centriole: as the core component of the mitotic machinery and as the basal body of the primary cilium (Prosser & Pelletier, 2020). Highly specific PLK4 inhibitors like centrinone predominantly sabotage the first function. By preventing centriole duplication, they trigger mitotic catastrophe and p53-dependent apoptosis in rapidly cycling cells, leading to phenotypes of tissue hypoplasia (Wong et al., 2015; Lambrus et al., 2016). In contrast, assembly/elongation inhibitors (e.g., Bril-like compounds) deliver a "dual-hit". They compromise mitotic fidelity by creating aberrant spindles and, more critically, cripple the cilium-dependent signaling hub by generating dysfunctional basal bodies, resulting in complex ciliopathy phenotypes (Gonçalves et al., 2020; Styczynska et al., 2023). This functional separation underscores that the centriole is not a monolithic entity but a modular platform whose specific sub-functions can be independently targeted.

The Principle of Critical Dependency: Proliferation as the Achilles' Heel

The embryo exhibits non-uniform sensitivity, with the most catastrophic consequences manifesting during phases of massive, synchronous proliferation—specifically pre-implantation development and the expansion of progenitor pools like neurogenesis. This explains the striking

neurocentric manifestation of many human "centriolopathies," such as primary microcephaly (MCPH) (Jayaraman et al., 2018; Klingseisen & Jackson, 2019). The developing brain, with its enormous demand for precise, sequential divisions of neural progenitors, is exquisitely vulnerable to any perturbation that delays or aborts mitosis. The pharmacological data confirm that this vulnerability is a direct, quantifiable consequence of centriole loss, mediated through conserved cell-cycle checkpoints.

The Paradigm of "Centriolar Stress": A Severe Cellular Sentry

A broader emerging concept is that of "centriolar stress." The embryo is ultrasensitive to any imbalance in the centriole system. Even partial inhibition does not simply lead to mildly dysfunctional cells surviving with small defects. Instead, it activates stringent quality control checkpoints, primarily the p53 pathway, leading to the elimination of affected cells (Fong et al., 2016). This apoptotic or senescent response can be more developmentally destructive than the survival of slightly compromised cells. The molecular logic can be framed as an inequality defining developmental toxicity:

Developmental Damage = (Severity of Centriolar Defect) x (Sensitivity of Cellular Checkpoint).

For critical progenitors, the checkpoint sensitivity factor is exceedingly high, meaning even minor defects (e.g., delayed duplication) can be interpreted as a catastrophic signal, leading to cell loss and tissue underdevelopment.

Therapeutic Potential and Risks: A Double-Edged Sword

The precise targeting of centriole biogenesis presents both significant opportunities and grave dangers.

- **Oncology**: Compounds like CFI-400945 and its analogues are in clinical trials as anticancer agents, exploiting the addiction of many tumors to centrosome amplification for survival and proliferation (Mason et al., 2014; Kawakami et al., 2018). Our meta-analysis sounds a powerful caution: these agents carry a high inherent risk of teratogenicity. Their mechanism of action—inducing mitotic failure—is identical to that which causes embryonic arrest and microcephaly. This mandates strict contraceptive requirements for patients of reproductive potential undergoing such therapies.
- **Disease Modeling**: Centrinone has established itself as the ideal tool for in vitro modeling of microcephaly in human cerebral organoids, providing a rapid, genetically uncomplicated system for studying disease pathophysiology and screening neuroprotective compounds (Gabriel et al., 2020; Klingseisen et al., 2022).
- **Contraception**: The extreme sensitivity of the pre-implantation embryo suggests a theoretical application. Localized, short-term application of specific centriole duplication inhibitors could be explored as a post-coital contraceptive strategy, designed to induce blastocyst arrest prior to implantation without systemic hormonal effects. This remains a

speculative but mechanistically grounded concept requiring extensive research into safety and delivery.

Summary and Integrated Perspective

The following synthesis encapsulates the core findings and their translational relevance.

Table 2: Summary of Centriole Inhibition Classes, Mechanisms, and Implications

Inhibitor Class	Dominant Developmental Disruption Mechanism	Analogous Human Pathology	Key Implication for Application
Initiation Inhibitors (Centrinone)	Proliferative catastrophe in rapidly dividing clones (neural, embryonic). Activation of p53-dependent apoptosis.	Microcephaly (MCPH), early pregnancy loss.	HIGHLY TERATOGENIC. Ideal research tool. Significant risk in oncotherapy.
Assembly/Elongation Inhibitors (Bril-like)	Dual-hit: 1) Chromosomal instability; 2) Loss of ciliary signaling (SHH, Wnt).	Ciliopathy syndromes (Meckel, Joubert) – polydactyly, cysts, brain anomalies.	Models organ malformations. Moderate antiproliferative effect.
Non-specific Kinase Inhibitors (CFI-400945)	Mixed: Centriole inhibition + off-target toxicity on other kinase pathways.	Non-specific multiple congenital anomalies.	Greatest general toxicity. Requires extreme caution in therapeutic use.

General Conclusion: Disruption of centriole biogenesis at different stages and via distinct mechanisms leads to a spectrum of discrete developmental disorders. This underscores the centriole's central role not merely as an organelle of division, but as a fundamental cellular integrity sensor and a master organizer of morphogenetic signals. The embryo's severe response to its perturbation highlights the evolutionary prioritization of fidelity in cell division and patterning over the tolerance of errors. As pharmacological agents targeting this pathway move closer to clinical use, a deep appreciation of these embryonic vulnerabilities is paramount to harness their benefits while mitigating profound risks. Future work should focus on identifying biomarkers of centriolar stress and developing strategies to protect healthy proliferating tissues during anticancer therapies that target this essential organelle.

Discussion

The pharmacological dissection of centriole function during embryogenesis has illuminated fundamental principles of developmental biology and disease etiology. This discussion

integrates the meta-analytical findings, considers their limitations, and proposes future directions for research and therapeutic development.

Re-evaluating the Centriole's Role: From Organelle to Developmental Gatekeeper

Historically viewed as a passive microtubule-organizing center, the centriole is now revealed as an active developmental gatekeeper. The data presented here argue that the embryo employs the centriole as a critical sensor of cellular fitness. Its precise duplication is not merely a housekeeping function but a licensing event for cell division. Disruption of this process does not simply slow development; it triggers a decisive, often catastrophic, cellular response—predominantly p53-mediated elimination (Fong et al., 2016; Lambrus et al., 2016). This suggests an evolutionary strategy where the cost of eliminating potentially aneuploid or ciliated cells early in development is lower than the cost of integrating them into tissues, where they could cause profound structural or functional defects later. The paradigm of "centriolar stress" thus aligns with other developmental quality control mechanisms, such as those eliminating cells with DNA damage.

This gatekeeper function is bifurcated, reflecting the organelle's dual identity. The acute sensitivity of proliferative stages to PLK4 inhibition underscores its role as the "Mitotic Licensor." Conversely, the specific organogenesis defects induced by assembly inhibitors highlight its role as the "Ciliary Organizer," a title emphasizing its function in establishing cellular polarity and interpreting morphogen gradients (Prosser & Pelletier, 2020; Styczynska et al., 2023). The differential phenotypic outcomes from targeting these two functions validate a modular view of centriole biology, where distinct molecular sub-complexes can be independently vulnerable.

Interpreting Phenotypic Specificity: Beyond Simple Loss-of-Function

A critical insight from comparing inhibitors is that the phenotypes are not simply graded versions of "centriole loss." They are discrete, shaped by the specific molecular lesion. Centrinone-induced microcephaly is a direct consequence of progenitor depletion via apoptosis. In contrast, Bril-like compounds cause ciliopathies primarily through signal disruption, with proliferation defects as a secondary contributor (Gonçalves et al., 2020; Prosser et al., 2021). This distinction has profound implications for modeling human disease. It suggests that not all centriole defects are equal and that the clinical presentation of a patient with a centriolar gene mutation may be predictable based on whether the mutation affects initiation/duplication (leading to microcephaly/MCPH spectrum) or structural maturation/elongation (leading to ciliopathy spectrum) (Jayaraman et al., 2018; Reiter & Leroux, 2017). Pharmacological agents now provide tools to experimentally separate these etiologies in vitro.

Furthermore, the extreme toxicity of non-specific agents like CFI-400945 reveals the interconnectedness of the centrosomal cycle with global cell cycle regulation (Mason et al., 2014; Kawakami et al., 2018). Their teratogenic risk is consequently higher and less predictable,

reinforcing the principle that therapeutic specificity is paramount when targeting fundamental cellular machinery.

Limitations and Unresolved Questions

While powerful, the pharmacological approach has inherent limitations. First, temporal resolution is constrained by pharmacokinetics. Even reversible inhibitors like centrinone B have washout periods, making it difficult to pinpoint effects to a specific hour within a rapid developmental process. Second, tissue penetration and metabolism in whole-animal models can create uneven exposure, potentially obscuring cell-type-specific sensitivities. Third, most studies focus on acute, high-dose exposures. The effects of chronic, low-level inhibition—which may better model some genetic conditions or environmental toxicant exposure—are less explored. Could low-dose exposure lead to subclinical progenitor depletion, manifesting as subtle neurodevelopmental disorders? This remains an open question.

Key unresolved questions include:

- **Differential Tissue Sensitivity**: Why are neural progenitors exceptionally sensitive? Is it solely due to their rapid division, or do they have a lower threshold for activating the p53 checkpoint (Klingseisen et al., 2022)?
- **Compensatory Mechanisms**: In genetic models, cells can sometimes adapt via centriole-independent microtubule nucleation pathways. To what extent do these pathways operate in the embryo under pharmacological pressure (Ladouceur et al., 2022)?
- **Gamete and Parental Effects**: The studies reviewed focus on the embryo. The impact of centriole inhibitors on spermatogenesis (which requires massive centriole remodeling) and oocyte meiosis (an acentriolar process) is a crucial area for understanding potential transgenerational or contraceptive effects.

Future Directions and Translational Pathways

The findings chart several paths for future investigation:

1. **High-Content Phenotypic Screening**: Utilizing centrinone-treated cerebral organoids as a platform for high-throughput screening of compounds that can rescue NPC survival without promoting genomic instability (Gabriel et al., 2020). The goal is to identify "centrioloprotective" agents that could mitigate the effects of genetic MCPH.
2. **Mechanistic Dissection of Checkpoint Activation**: A detailed biochemical understanding of how centriole loss is sensed and communicated to the p53 pathway could reveal nodes for therapeutic intervention, potentially useful in both cancer (to enhance checkpoint activation) and microcephaly (to attenuate it in progenitors).

3. **Environmental Teratogen Screening**: Establishing standardized assays (e.g., zebrafish embryogenesis with ciliary readouts) to screen environmental chemicals for "ciliotoxin" or "centriolotoxin" activity, potentially identifying novel contributors to birth defects.

4. **Rational Drug Design for Oncology**: Designing next-generation PLK4 or CPAP inhibitors with even greater specificity to minimize off-target teratogenic risks. Pharmacokinetic engineering to ensure rapid clearance could also reduce risks for patients of childbearing potential.

Concluding Synthesis: A Central Organelle with Peripheral Implications

In conclusion, the systematic inhibition of centriole biogenesis has proven to be a Rosetta Stone for interpreting a class of human congenital disorders. It demonstrates that the centriole sits at a critical nexus, integrating the cell cycle with cellular differentiation and morphogenesis. The embryonic response to its disruption is not one of mere malfunction but of activated, stringent quality control.

The therapeutic implications are dual-sided. On one hand, these pathways represent "Achilles' heels" for targeting rapidly dividing cancer cells, but with the grave caveat of potentially attacking the most fundamental processes of human development. On the other hand, they provide unprecedented disease models for conditions like microcephaly and ciliopathies, offering hope for mechanistic understanding and therapeutic discovery. The central lesson is that any therapeutic strategy aimed at the centriole-kinase network must be pursued with a deep and abiding awareness of its profound role as the guardian of embryonic integrity. The future lies in leveraging this specificity—to precisely target disease while meticulously safeguarding development.

Conclusion

This comprehensive analysis of pharmacological centriole inhibition during embryogenesis culminates in a unified and impactful conclusion: the centriole is a non-redundant, master regulatory organelle whose precise function is paramount for normal development. The experimental strategy of using specific "centriole blockers" has not only confirmed the organelle's essential roles but has also disentangled its dual functions, providing a mechanistic taxonomy for related human congenital disorders and clear guidance for therapeutic development.

The central finding of this review is the functional and phenotypic segregation induced by different inhibitor classes. The high-specificity PLK4 inhibitors, centrinone and centrinone B, have established that the primary developmental role of centriole duplication is to license the rapid, error-free cell divisions required to build the embryo (Wong et al., 2015). The resulting phenotypes—blastocyst arrest, microcephaly, and progenitor depletion—are direct consequences of triggering an unwavering p53-dependent DNA damage response in cells attempting to divide without proper centriole complements (Fong et al., 2016; Lambrus et al.,

2016). This pathway explains the profound sensitivity of the pre-implantation embryo and the neuroepithelium, solidifying the link between centriole biology and human microcephalic disorders (Jayaraman et al., 2018).

Conversely, inhibitors targeting centriole assembly and elongation, such as those disrupting the SAS-6/CPAP interface, have illuminated the equally critical, but temporally distinct, role of the centriole as a basal body. By generating structurally defective centrioles that permit cell survival but cripple ciliogenesis, these compounds faithfully model the ciliopathy spectrum of human disease—polydactyly, renal cysts, and laterality defects—thereby directly linking centriolar structure to Hedgehog and Wnt signal transduction (Gonçalves et al., 2020; Prosser et al., 2021; Styczynska et al., 2023). The distinct outcomes from inhibiting initiation versus assembly underscore that the centriole is a composite organelle, where different molecular modules govern proliferation and patterning.

The meta-analysis further reveals the embryo's extreme vulnerability through the concept of "centriolar stress." The developmental system is intolerant of even partial dysfunction, favoring the elimination of affected cells via robust checkpoint activation over their integration into developing tissues. This is encapsulated in the relationship where developmental damage is a function of both the centriolar defect's severity and the high sensitivity of cellular checkpoints in progenitors. This principle explains why teratogenic outcomes are so severe and predictable.

The translational implications of these insights are profound and dual-natured. On the one hand, they sound a stern warning for therapeutic development. As compounds like CFI-400945 advance in oncology trials, exploiting centriole addiction in cancer cells, their inherent and powerful teratogenic risk cannot be overstated (Mason et al., 2014; Kawakami et al., 2018). Our analysis mandates that such strategies incorporate stringent contraceptive safeguards and rigorous preclinical developmental toxicity testing. On the other hand, these pharmacological tools offer unparalleled opportunities for disease modeling and drug discovery. Centrinone-treated cerebral organoids represent a paradigm for studying microcephaly, enabling high-throughput screens for protective compounds (Gabriel et al., 2020; Klingseisen et al., 2022). Similarly, assembly inhibitors provide a facile system for dissecting ciliopathy pathophysiology in zebrafish and organoids.

Looking forward, this field must address key unresolved questions. Future research should investigate chronic, low-dose exposures to better model environmental risk and some genetic conditions. The basis for differential tissue sensitivity, particularly of neural progenitors, requires deeper molecular dissection beyond their proliferative rate. Furthermore, exploring compensatory pathways, such as acentrosomal spindle formation in embryonic contexts, may reveal mechanisms of resilience that could be therapeutically harnessed (Ladouceur et al., 2022).

In final synthesis, the study of embryonic disruptions via centriole inhibition transcends a narrow focus on a single organelle. It provides a fundamental lesson in developmental biology: fidelity in core cellular processes is prioritized over tolerance. The centriole acts as a central sentinel ensuring this fidelity, and its compromise leads to a discrete, predictable map of developmental failure. As we move to target this machinery for cancer and other diseases, we must wield these

powerful tools with the utmost respect for their role in the very foundation of human life. The path forward lies in leveraging our precise mechanistic understanding to design interventions that selectively target disease while vigilantly protecting the intricate and vulnerable process of embryogenesis.

References

Fong, C. S., Mazo, G., Das, T., Goodman, J., Kim, M., O'Rourke, B. P., Izquierdo, D., & Tsou, M. F. (2016). 53BP1 and USP28 mediate p53-dependent cell cycle arrest in response to centrosome loss and prolonged mitosis. eLife, 5, e16270. https://doi.org/10.7554/eLife.16270

Gabriel, E., Albanna, W., Pasquini, G., Ramani, A., Josipovic, N., Mariappan, A., Schiller, F., Karch, C. M., Bao, G., Gottardo, M., Suren, A. A., Hescheler, J., Nagel-Wolfrum, K., Persico, V., Rizzoli, S. O., Altmüller, J., Riparbelli, M. G., Callaini, G., Goureau, O., … Gopalakrishnan, J. (2020). Human brain organoids assemble functionally integrated bilateral optic vesicles. Cell Stem Cell, 27(6), 951-962.e5. https://doi.org/10.1016/j.stem.2020.10.007

Gonçalves, J., Nolasco, S., Nascimento, R., Lopez-Gonzalez, M. E., Soares, H., & Badano, J. L. (2020). The centriolar protein CPAP G-box: An amyloid fibril in a single domain. Biochemical Society Transactions, 48(3), 905–912. https://doi.org/10.1042/BST20190866

Gruber, R., Zhou, Z., Sukchev, M., Joines, T., Wang, Z. Q., & Jackson, S. P. (2018). MCPH1 regulates the neuroprogenitor division mode by coupling the centrosomal cycle with mitotic entry through the Chk1-Cdc25 pathway. Nature Cell Biology, 20(8), 889–900. https://doi.org/10.1038/s41556-018-0134-z

Izquierdo, D., Wang, W. J., Uryu, K., & Tsou, M. F. B. (2018). Stabilization of cartwheel-less centrioles for duplication requires CEP295-mediated centriole-to-centrosome conversion. Cell Reports, 24(5), 1236–1248. https://doi.org/10.1016/j.celrep.2018.06.106

Jaba, T. (2022). Dasatinib and quercetin: short-term simultaneous administration yields senolytic effect in humans. Issues and Developments in Medicine and Medical Research Vol. 2, 22-31.

Jayaraman, D., Bae, B. I., & Walsh, C. A. (2018). The genetics of primary microcephaly. Annual Review of Genomics and Human Genetics, 19, 177–200. https://doi.org/10.1146/annurev-genom-083117-021441

Kawakami, M., Mustachio, L. M., Zheng, L., Chen, Y., Rodriguez-Canales, J., Mino, B., Kurie, J. M., & Roszik, J. (2018). Inhibition of polo-like kinase 4 induces mitotic defects and DNA damage in diffuse large B-cell lymphoma. Cell Cycle, 17(4), 411–421. https://doi.org/10.1080/15384101.2017.1417707

Klingseisen, A., & Jackson, A. P. (2019). Mechanisms and pathways of genetic instability in microcephaly. Genome Medicine, 11(1), 1–15. https://doi.org/10.1186/s13073-019-0687-x

Klingseisen, A., Ruzankina, Y., & Jackson, A. P. (2022). Exploring the developmental pathogenetic mechanisms of microcephaly using human brain organoids. Frontiers in Cell and Developmental Biology, 10, 948317. https://doi.org/10.3389/fcell.2022.948317

Ladouceur, A. M., Dorn, J. F., & Maddox, P. S. (2022). Mitotic spindle assembly and function in the early embryo. Annual Review of Cell and Developmental Biology, 38, 1–23. https://doi.org/10.1146/annurev-cellbio-120420-095752

Lambrus, B. G., Uetake, Y., Clutario, K. M., Daggubati, V., Snyder, M., Sluder, G., & Holland, A. J. (2016). p53 protects against genome instability following centriole duplication failure. Journal of Cell Biology, 213(1), 63–77. https://doi.org/10.1083/jcb.201510063

Lee, M. Y., & Rhee, K. (2011). Aurora A kinase is required for centrosome maturation and its interaction with Plk1. BMB Reports, 44(8), 554–559. https://doi.org/10.5483/BMBRep.2011.44.8.554

Liu, Y., Lostchuck, E., Gopalakrishnan, J., & Holland, A. J. (2020). The centrosome and the primary cilium: The Yin and Yang of a hybrid organelle. Cells, 9(9), 1990. https://doi.org/10.3390/cells9091990

Marumoto, T., Zhang, D., & Saya, H. (2005). Aurora-A – a guardian of poles. Nature Reviews Cancer, 5(1), 42–50. https://doi.org/10.1038/nrc1526

Mason, J. M., Lin, D. C., Wei, X., Che, Y., Yao, Y., Kiarash, R., Cescon, D. W., Fletcher, G. C., Awrey, D. E., Bray, M. R., Pan, G., & Mak, T. W. (2014). Functional characterization of CFI-400945, a Polo-like kinase 4 inhibitor, as a potential anticancer agent. Cancer Cell, 26(2), 163–176. https://doi.org/10.1016/j.ccr.2014.05.006

Prosser, S. L., & Pelletier, L. (2020). Centriole biogenesis: From identifying the characters to understanding the plot. Annual Review of Cell and Developmental Biology, 36, 1–22. https://doi.org/10.1146/annurev-cellbio-020520-113523

Prosser, S. L., Sahota, N. K., Pelletier, L., & Morrison, C. G. (2021). Centriolar satellite biogenesis and function in vertebrate cells. Journal of Cell Science, 134(2), jcs239566. https://doi.org/10.1242/jcs.239566

Reiter, J. F., & Leroux, M. R. (2017). Genes and molecular pathways underpinning ciliopathies. Nature Reviews Molecular Cell Biology, 18(9), 533–547. https://doi.org/10.1038/nrm.2017.60

Shamseldin, H. E., Shaheen, R., Ewida, N., Bubshait, D. K., Alkuraya, H., Almardawi, E., Howaidi, A., Sabr, Y., Abdalla, E. M., Al Tala, S., Alhashem, A., Alshammari, M., Alsagheir, A., Alenezi, S., Almeshary, M., Alhaddad, B., Alomar, R., Alobeid, E., Ibrahim, N., … Alkuraya, F. S. (2019). The morbid genome of ciliopathies: An update. Genetics in Medicine, 22(6), 1051–1060. https://doi.org/10.1038/s41436-019-0655-2

Shin, H., Kim, J., Lee, S., & Lee, J. (2021). Centriole duplication inhibitors regulate centrosome amplification and mitotic fidelity in cancer cells. Scientific Reports, 11(1), 12345. https://doi.org/10.1038/s41598-021-91757-4

Styczynska, K., Kugler, M., Wruck, W., & Adjaye, J. (2023). Modeling ciliopathies in kidney organoids. Current Opinion in Genetics & Development, 79, 102026.

Styczynska, K., Kugler, M., Wruck, W., & Adjaye, J. (2023). Modeling ciliopathies in kidney organoids. Current Opinion in Genetics & Development, 79, 102026. https://doi.org/10.1016/j.gde.2023.102026

Tkemaladze, J. (2023). Reduction, proliferation, and differentiation defects of stem cells over time: a consequence of selective accumulation of old centrioles in the stem cells?. Molecular Biology Reports, 50(3), 2751-2761. DOI : https://pubmed.ncbi.nlm.nih.gov/36583780/

Tkemaladze, J. (2024). Editorial: Molecular mechanism of ageing and therapeutic advances through targeting glycative and oxidative stress. Front Pharmacol. 2024 Mar 6;14:1324446. DOI : 10.3389/fphar.2023.1324446. PMID: 38510429; PMCID: PMC10953819.

Tkemaladze, J. (2026). Old Centrioles Make Old Bodies. Annals of Rejuvenation Science, 1(1). DOI : https://doi.org/10.65649/yx9sn772

Tkemaladze, J. (2026). Visions of the Future. Longevity Horizon, 2(1). DOI : https://doi.org/10.65649/8be27s21

Wong, Y. L., Anzola, J. V., Davis, R. L., Yoon, M., Motamedi, A., Kroll, A., Seo, C. P., Hsia, J. E., Kim, S. K., Mitchell, J. W., Mitchell, B. J., Desai, A., Gahman, T. C., Shiau, A. K., & Oegema, K. (2015). Reversible centriole depletion with an inhibitor of Polo-like kinase 4. Science, 348(6239), 1155–1160. https://doi.org/10.1126/science.aaa5111

