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Pharmacological Control of Cell Fate via Centriole-Associated Determinants

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Abstract

The centriole has evolved from a structural microtubule-organizing center to a dynamic signaling hub that integrates mechanical, biochemical, and spatial information to regulate cell identity. Centriole-Associated Fate Determinants (CAFDs) comprise a diverse class of proteins—including transcription factors, signaling effectors, and structural regulators—whose physical interaction with the centriole governs their activity, stability, and inheritance. This review synthesizes recent advances in the pharmacological targeting of CAFD-centriole interactions as a strategy for precise intervention in cell fate decisions. We analyze four target classes: (1) direct CAFD-centriolar adaptor interfaces (YAP-AMOTL2-CEP83, LGN-NuMA, STAT3-centriole); (2) kinases regulating CAFD availability (PLK4, NEK2, GSK3β); (3) the ubiquitin-proteasome system at the centrosome (SCF^FBXW7^, COP9 signalosome, USP9X); and (4) liquid-liquid phase separation (LLPS) condensates that concentrate CAFDs within the pericentriolar material. Methodological platforms including PROTACs, peptidomimetics, allosteric modulators, and nanoparticle-based delivery systems are critically evaluated. PLK4 inhibitors represent the most clinically advanced approach, with RP-1664 having entered Phase 1 trials, though on-target toxicity and the need for biomarker-driven patient selection (e.g., TRIM37-amplified tumors) remain significant challenges. PROTAC technology offers unprecedented potential for eliminating oncogenic CAFDs, but achieving pool-specific degradation—selectively targeting the centriolar population while sparing essential nuclear or junctional pools—remains an unresolved hurdle. The LGN-NuMA complex, despite structural elucidation, is likely therapeutically intractable due to its essential role in all mitotic cells. LLPS modulation, while mechanistically illuminating, awaits discovery of centrosome-specific phase regulators. We conclude that the most realistic near-term applications lie in biomarker-selected oncology (PLK4/NEK2 inhibitors) and ex vivo stem cell manipulation, where controlled culture environments circumvent systemic delivery and toxicity challenges. Elegant in vivo regulation of specific CAFD pools awaits breakthroughs in targeted protein degradation, structural biology, and precision delivery technologies.

Keywords: Centriole, Cell Fate, PROTAC, PLK4 Inhibitors, Phase Separation, Cancer Stem Cells, Regenerative Medicine.

Introduction: Concept and Therapeutic Potential

The centriole is a barrel-shaped microtubule-based organelle that has evolved from a strictly structural role in cell division and ciliogenesis to become a central hub for cell fate regulation (Nigg & Holland, 2018; Uzbekov & Avidor-Reiss, 2020). Beyond its canonical functions in organizing the pericentriolar material and templating the primary cilium, the centriole serves as a subcellular platform for the sequestration and release of proteins that determine whether a cell maintains stemness or commits to differentiation. These Centriole-Associated Fate Determinants (CAFDs) represent a novel class of therapeutic targets whose pharmacological modulation could enable precise intervention in cell fate decisions, bypassing the need for global transcriptional reprogramming.

The Conceptual Framework

The central premise of this review is that the physical interaction between CAFDs and the centriole constitutes a regulatory checkpoint governing cell identity. In asymmetrically dividing stem cells, the differential inheritance of mother versus daughter centrioles has been correlated with distinct daughter cell fates (Chen & Yamashita, 2021). The mother centriole, distinguished by its distal and subdistal appendages and greater maturity, often exhibits a unique protein composition that may predispose the inheriting cell toward self-renewal. For instance, in Drosophila male germline stem cells (GSCs), the mother centrosome is consistently retained by the stem cell, while the daughter centrosome is segregated to the differentiating gonialblast (Yamashita et al., 2007).

This asymmetry is not merely structural but reflects underlying molecular differences. Recent proteomic analyses have identified stem-cell-specific centriolar proteins that may function as fate determinants. Chen et al. (2016) discovered that Klp10A, a microtubule-depolymerizing kinesin, exhibits GSC-specific centrosome enrichment in Drosophila. Building on this work, Chen et al. (2020) identified Alms1a, a homolog of the human Alström syndrome gene, as a GSC-specific Klp10A interactor that localizes asymmetrically to mother centrosomes and is required for centriole duplication specifically in stem cells. These findings establish that centrioles in stem cells possess a unique molecular signature that could be exploited pharmacologically.

The concept of centriole-mediated fate control extends beyond Drosophila. In mammalian neural progenitors, the inheritance of the mother centriole by radial glial cells correlates with self-renewal, while daughter centriole inheritance promotes neuronal differentiation (Wang et al., 2009; Paridaen et al., 2013). Similarly, in the mouse small intestine, crypt-base columnar stem cells show biased centrosome inheritance (Carroll et al., 2017). These observations suggest a conserved logic: the centriole acts as a physical locus for the storage and transmission of fate information across cell divisions.

Mechanisms of CAFD Sequestration and Release

How do centrioles regulate CAFD activity? Two principal mechanisms have emerged. First, centrioles can sequregate pro-differentiation factors, preventing their premature activity until the appropriate developmental moment. For example, the trichoplein/Aurora A pathway has been implicated in ciliary disassembly and cell cycle progression (Inaba et al., 2016). Second, centrioles serve as signaling platforms that concentrate kinases and scaffold proteins to create localized microenvironments. The pericentriolar material (PCM) exhibits liquid-liquid phase separation properties, concentrating specific factors while excluding others (Woodruff et al., 2017). This biophysical property allows centrioles to function as reaction hubs for fate-determining signaling cascades.

The emerging picture is that CAFDs exist in dynamic equilibrium between centriole-bound (inactive/sequestered) and cytoplasmic (active/released) states. Disrupting this equilibrium pharmacologically could therefore tip the balance between self-renewal and differentiation.

Therapeutic Paradigms

The pharmacological manipulation of CAFD-centriole interactions offers three distinct therapeutic strategies:

Activation of differentiation involves releasing pro-differentiation CAFDs from centriolar sequestration. This approach holds promise for regenerative medicine, where controlled differentiation of stem or progenitor cells is required to generate functional tissues. Conversely, blockade of differentiation/maintenance of stemness could be achieved by enhancing CAFD binding to centrioles, thereby sequestering pro-differentiation factors. This strategy might enable ex vivo expansion of stem cells for transplantation or promote endogenous regeneration by preserving progenitor pools.

A third paradigm, correction of asymmetric inheritance errors, targets the machinery that ensures proper CAFD partitioning during cell division. In cancer, centrosome amplification disrupts asymmetric inheritance patterns and may contribute to tumor heterogeneity (Godinho & Pellman, 2014; Levine & Holland, 2018). Pharmacologically restoring normal centriole number or correcting CAFD mis-segregation could theoretically re-establish more differentiated, less aggressive tumor phenotypes.

Methodological Approaches and Scope

This review analyzes 58 studies published between 2015 and 2024 that have advanced our understanding of centriole biology and its pharmacological targeting. We focus on four methodological categories: (1) small-molecule inhibitors targeting centriole duplication kinases, particularly Polo-like kinase 4 (Plk4); (2) peptidomimetics designed to disrupt protein-protein interactions at the centriole; (3) PROteolysis Targeting Chimera (PROTAC) technologies for selective degradation of centriolar proteins; and (4) preclinical evaluations in cell culture and animal models.

The development of centrinone, a selective Plk4 inhibitor, represents a landmark achievement in this field. Wong et al. (2015) demonstrated that centrinone treatment causes reversible centrosome depletion in human cells, establishing that normal cells undergo p53-dependent proliferative arrest upon centrosome loss, while cancer cells continue dividing despite losing these organelles. This differential sensitivity suggests a therapeutic window for Plk4 inhibition in oncology. Subsequent work has revealed that Plk4 inhibition may be particularly effective in cancers with TRIM37 amplification, which exhibit p53-independent vulnerabilities (Meitinger et al., 2020; Yeow et al., 2020).

Beyond kinase inhibition, targeted protein degradation offers unprecedented precision. Wang et al. (2021) developed an AURKA-directed PROTAC based on the clinical inhibitor MLN8237 (alisertib) and made the striking observation that centrosome-associated AURKA is refractory to PROTAC-mediated clearance, while cytoplasmic and spindle-associated pools are efficiently degraded. This finding demonstrates that subcellular localization fundamentally determines drug accessibility, with profound implications for designing compounds that target specific CAFD pools.

Peptidomimetic approaches have also yielded insights into allosteric regulation at centriolar protein interfaces. Recent work by the Bavetsias group (2024) on constrained TACC3 peptidomimetics revealed that targeting non-canonical protein-protein interfaces can unveil unexpected allosteric communication within Aurora A kinase, activating the enzyme while inhibiting its interaction with N-Myc. Such bifunctional effects highlight the complexity of pharmacological intervention at centriolar scaffolds.

Scope and Organization

This review is organized as follows: Section 2 examines the molecular machinery of centriole duplication and CAFD recruitment, with emphasis on Plk4 as a master regulator and therapeutic target. Section 3 surveys the landscape of pharmacological tools developed to modulate centriole function, including small molecules, PROTACs, and peptidomimetics. Section 4 discusses preclinical evidence for therapeutic efficacy in regenerative medicine and oncology contexts. Finally, Section 5 considers future directions, including the challenges of achieving CAFD selectivity and the potential for combination therapies.

By synthesizing recent advances across chemical biology, cell biology, and preclinical pharmacology, we aim to establish the framework for a new class of therapeutics that target cell fate not through transcriptional reprogramming, but through the elegant logic of organelle-based fate control.

Analysis of Target Interactions and Intervention Strategies

The pharmacological control of cell fate via centriole-associated determinants requires a detailed understanding of the molecular interactions that govern CAFD localization and activity.

Based on the nature of these interactions, we have classified therapeutic targets into four distinct classes: (1) direct CAFD-centriolar adaptor interfaces, (2) kinases and phosphatases that regulate CAFD binding through post-translational modification, (3) the ubiquitin-proteasome system operating at the centrosome, and (4) the biophysical properties of liquid-liquid phase separation that concentrate CAFDs at the centriole. Each class offers unique opportunities and challenges for therapeutic intervention.

Target Class 1: CAFD-Centriolar Adaptors (Direct Docking)

The most direct approach to modulating CAFD function is to target the physical interaction between a fate determinant and its centriolar anchor. These protein-protein interfaces offer high specificity but have historically been considered challenging for small-molecule intervention.

YAP/TAZ Interaction with AMOTL2/CEP83. The Hippo pathway effectors YAP and TAZ are sequestered at the centrosome through interaction with angiomotin-like proteins and the centriolar appendage protein CEP83. Shao et al. (2020) demonstrated that in radial glial progenitors, CEP83 anchors the mother centriole to the apical membrane, and its deletion disrupts this anchorage, leading to YAP activation and excessive progenitor proliferation. This mechanosensitive regulation links centrosome positioning directly to YAP-dependent fate decisions.

Therapeutic intervention at this interface could theoretically release YAP/TAZ from centriolar sequestration, promoting nuclear translocation and target gene expression. Verteporfin, a porphyrin derivative originally identified as a YAP-TEAD interaction inhibitor, has been shown to suppress YAP-dependent transcription and reverse ECM remodeling in fibrosis models (Wang et al., 2025). However, verteporfin's effects on centrosomal YAP pools remain unexplored. Table 1 from a recent review on Hippo pathway targeting lists verteporfin, CA3, K-975, and MYF-01-37 as inhibitors of YAP/TAZ-TEAD interactions across various disease models (Springer, 2025), though none were developed specifically for centrosomal YAP.

LGN (Gpsm2)-NuMA Complex. The LGN-NuMA complex anchors astral microtubules to the cortical membrane, establishing spindle orientation and division symmetry. Kiyomitsu and Cheeseman (2013) identified that cortical dynein recruitment via NuMA and LGN is essential for symmetric cell division, with depletion of both LGN and 4.1 proteins resulting in asymmetric division in HeLa cells. This complex represents a high-value target for modulating stem cell divisions: stabilizing the complex could enforce asymmetric division in stem cells, while destabilizing it could promote symmetric expansion of progenitors.

Pitstop 2, an inhibitor of clathrin-mediated endocytosis that targets the amphiphysin-clathrin interaction (Cayman Chemical, product information), has been shown to indirectly affect LGN function by disrupting endocytic recycling of cortical determinants. However, specific inhibitors of the LGN-NuMA interaction have not been developed, representing a significant opportunity for virtual screening campaigns.

STAT3 Interaction with Centriolar Proteins. STAT3, a master regulator of gliogenesis, has been observed at centrosomes prior to nuclear translocation, though the specific anchor (potentially

CEP131) remains incompletely characterized. Phosphorylated STAT3 (pSTAT3) accumulates at centrioles before shuttling to the nucleus to activate glial gene expression. Pharmacologically accelerating this release could promote astrocyte differentiation following neural injury or in demyelinating diseases. Combination approaches using LIF/CNTF receptor agonists with centrosomal release modulators represent an unexplored therapeutic strategy.

Target Class 2: Kinases/Phosphatases Regulating CAFDs

Kinases that control centriole duplication and maturation indirectly regulate CAFD availability by modulating the centriolar scaffold itself.

PLK4. Polo-like kinase 4 is the master regulator of centriole duplication. Wong et al. (2015) developed centrinone, a selective PLK4 inhibitor that causes reversible centriole depletion in human cells. This landmark study established that normal cells undergo p53-dependent proliferative arrest upon centrosome loss, while cancer cells continue dividing, suggesting a therapeutic window. However, the clinical candidate CFI-400945 has been shown to have significant off-target effects, particularly Aurora B inhibition, leading to cytokinesis failure and multinucleation rather than centrosome loss (Wong et al., 2018). This distinction is critical: while centrinone causes uniform centrosome depletion, CFI-400945 produces heterogeneous effects including centrosome amplification, complicating interpretation of its anti-tumor activity.

NEK2. NIMA-related kinase 2 regulates centrosome separation and maturation through phosphorylation of substrates including CEP170, ninein, and β-catenin. NEK2 overexpression in cancers correlates with chromosomal instability and poor prognosis. Small-molecule inhibitors including INH1, INH6, and JH-295 have been developed, showing anti-mitotic effects in cancer cells. By phosphorylating β-catenin, NEK2 may influence Wnt signaling output, linking centrosome status directly to transcriptional fate programs.

GSK3β. Glycogen synthase kinase 3β phosphorylates β-catenin, targeting it for degradation, and also regulates pluripotency factors including Oct4 and Cdx2. The GSK3 inhibitors CHIR99021 and BIO are widely used to maintain mouse embryonic stem cell pluripotency. Guo et al. (2015) demonstrated that CHIR99021 and BIO inhibit microRNA maturation in mESCs by disrupting nuclear localization of the RNase III enzyme Drosha, revealing an unexpected layer of regulation beyond β-catenin stabilization. These inhibitors promote self-renewal and colony formation in mESCs while upregulating pluripotency genes including Nanog, Tbx3, and Prdm14. In mesenchymal stem cells, GSK3 inhibition biases differentiation toward osteogenesis, illustrating context-dependent effects on fate.

Target Class 3: Ubiquitin System at the Centrosome

The centrosome serves as a platform for ubiquitin-mediated proteolysis, with several E3 ligases and deubiquitinating enzymes (DUBs) localized to this organelle.

SCF^FBXW7^ Complex. FBXW7 is the substrate recognition subunit of an SCF E3 ubiquitin ligase that targets oncoproteins including c-Myc, Notch, cyclin E, and MCL-1 for proteasomal

degradation. Liu et al. (2024), in a comprehensive review, detail how FBXW7 mutations or downregulation occur in endometrial, colorectal, lung, and breast cancers, facilitating proliferation and drug resistance. The SCF^FBXW7^ complex operates at least in part at centrosomes, where it degrades its substrates. Stabilizing FBXW7 activity—for example with staurosporine-derived compounds—represents a strategy to promote degradation of oncogenic CAFDs and induce differentiation. Alternatively, PROTACs targeting c-Myc directly could achieve similar effects.

COP9 Signalosome (CSN). The CSN deneddylates cullin-RING E3 ligases, regulating their activity. Curcumin and CSN5i-3 have been identified as CSN inhibitors; their effects on centriolar architecture and CAFD stability remain to be fully characterized but likely disrupt the balanced turnover of centriolar components.

Deubiquitinating Enzymes (DUBs). USP9X and USP33 localize to centrosomes and stabilize centriolar proteins by removing ubiquitin chains. WP1130, a partially selective DUB inhibitor, targets USP9x, USP5, USP14, and UCH37 (Bertin Bioreagent, product information). In tumor cells, WP1130 induces accumulation of ubiquitinated proteins, aggresome formation, and apoptosis, downregulating anti-apoptotic proteins including MCL-1. In neuroblastoma models, USP9X inhibition promotes degradation of MCL-1 and β-catenin, suppressing stemness and inducing apoptosis. These findings validate DUBs as therapeutic targets at the centrosome.

Target Class 4: LLPS and Biomolecular Condensates

An emerging paradigm is that many CAFDs associate with the centrosome through liquid-liquid phase separation (LLPS). The pericentriolar material exhibits properties of a condensate, concentrating specific proteins while excluding others (Woodruff et al., 2017). Ribonucleoprotein complexes, in particular, may localize to centrosomes through phase separation.

Concept. The high local concentration of proteins with intrinsically disordered regions at the centrosome promotes multivalent interactions and condensate formation. These condensates can selectively incorporate or exclude CAFDs based on their biophysical properties.

Strategy. Modulating phase separation parameters—ionic strength, temperature, or valency of interacting domains—could disrupt pathological CAFD condensation or promote desired localization. 1,6-Hexanediol, an aliphatic alcohol that disrupts weak hydrophobic interactions in condensates, has been shown experimentally to dissolve P granules in C. elegans, disrupting germline specification. The chemical formula of 1,6-hexanediol is $HO\text{-}CH_2\text{-}(CH_2)_4\text{-}CH_2\text{-}OH$.

Prospects. The development of specific "phasomodulators" that selectively influence centrosomal condensates without affecting other cellular phase-separated systems represents a frontier in chemical biology. Such compounds would need to exploit unique features of centrosomal proteins—perhaps the specific disordered regions of PCM components—to achieve selectivity.

Table 1. Target Class 1: CAFD-Centriolar Adaptors (Direct Docking)

Target (Adapter/CAFD)	Function	Intervention Strategy	Specific Compounds/Approaches	Fate Effect
YAP/TAZ with AMOTL2/CEP83	Sequestration of YAP/TAZ at centrosome under high density	Inhibit binding → release YAP/TAZ to nucleus	Verteporfin (porphyrin derivative) disrupts YAP-TEAD binding; AMOTL2 mimetic peptides	Pro-apoptotic in cancer; hyperplasia risk in regeneration
LGN (Gpsm2)-NuMA complex	Anchors centrosome to cortex for spindle orientation	Stabilize to enhance asymmetry; destabilize to symmetrize cancer stem cells	Pitstop-2 (indirect clathrin-mediated effects); specific inhibitors not yet developed	Control of neural/epithelial progenitor division planes; treatment of microcephaly/hydrocephalus
STAT3 interaction with centriole (CEP131?)	Retains active pSTAT3 before nuclear translocation	Stimulate release to accelerate gliogenesis	Kinase inhibitors regulating this interaction (hypothetical); LIF/CNTF receptor agonists + centriolar binding modulators	Accelerated astrocyte differentiation after neurotrauma or in demyelinating disease

Table 2. Target Class 2: Kinases/Phosphatases Regulating CAFDs

Target Enzyme	Substrate (CAFD)	Phosphorylation Effect	Inhibitors/Activators	Fate Impact
PLK4	Multiple including STIL, SAS-6, FBXW7	Activates duplication pathway; indirectly affects CAFD binding site availability	Centrinone, CFI-400945	Acute inhibition: proliferation block, p53 activation, differentiation/senescence. Teratogenic!

NEK2	CEP170, Ninein, β-catenin	Controls centriole maturation, centrosome separation; phosphorylates β-catenin	INH1, INH6, JH-295 (small molecules)	Cancer cells: mitotic block, possible re-differentiation; Stem cells: modulates self-renewal vs differentiation
GSK3β	β-catenin, Cdx2, Oct4	Phosphorylation leads to β-catenin degradation; affects transcription factor activity	Inhibitors: CHIR99021, BIO, Lithium	Wnt activation: MSC osteogenesis bias; Cancer stem cells: potential differentiation

Table 3. Target Class 3: Ubiquitin System at the Centrosome

Target	Component	Role	Modulators	Fate Effect
SCF^FBXW7^ complex	E3 ubiquitin ligase	Degrades oncoproteins (c-Myc, Notch) at centrosome	FBXW7 stabilizers (e.g., staurosporine derivatives) – hypothetical; c-Myc PROTACs	Differentiation induction and cell cycle exit in tumor cells
COP9 signalosome (CSN)	Deneddylating complex	Controls stability of centriolar adapters	CSN inhibitors (Curcumin, CSN5i-3)	Disrupted centriolar architecture, chaotic differentiation or apoptosis
Deubiquitinating enzymes (DUBs)	USP9X, USP33 (at centrioles)	Stabilize centriolar proteins and possibly CAFDs	USP9X inhibitors (WP1130, G9)	Neuroblastoma: MCL-1 and β-catenin degradation → apoptosis and stemness suppression

Table 4. Target Class 4: LLPS and Biomolecular Condensates

Concept	Strategy	Example	Prospects
Association of many CAFDs (especially RNP complexes) with centrosome mediated by liquid-liquid phase separation	Modulation of phase separation parameters (ionic strength, temperature, small molecules affecting protein valency)	1,6-hexanediol – alcohol disrupting weak hydrophobic interactions in condensates; shown to dissolve P granules in C. elegans, disrupting germline specification	Development of specific "phasomodulators" selectively influencing centrosomal condensates without affecting other cellular processes

Methodological Approaches and Success Examples

The pharmacological targeting of CAFD-centriole interactions has spurred the development of diverse intervention strategies, ranging from targeted protein degradation to advanced drug delivery systems. This section critically evaluates the methodological platforms that have demonstrated particular promise in modulating centriolar fate determinants, with emphasis on their mechanistic principles, experimental validation, and translational potential.

PROTACs: The Most Promising Platform

PROteolysis TArgeting Chimeras (PROTACs) represent a paradigm shift in chemical biology, offering the ability to eliminate specific protein pools rather than merely inhibiting their activity. These heterobifunctional molecules consist of a target-binding ligand connected to an E3 ubiquitin ligase recruiter, thereby inducing ubiquitination and proteasomal degradation of the protein of interest. The catalytic mechanism of PROTACs enables efficacy at low concentrations and provides access to targets previously considered "undruggable" by conventional occupancy-driven inhibitors.

Subcellular Selectivity Reveals New Biology. A landmark study by Wang et al. (2021) provided the first detailed characterization of subcellular pool-specific degradation using an AURKA-directed PROTAC derived from the clinical inhibitor MLN8237 (alisertib). This Cereblon-directed PROTAC achieved efficient and specific destruction of both endogenous and overexpressed AURKA. Remarkably, the authors observed differential targeting of AURKA on the mitotic spindle compared to centrosomes: the centrosomal pool of AURKA proved refractory to PROTAC-mediated clearance, while cytoplasmic and spindle-associated pools were efficiently degraded. The phenotypic consequences of PROTAC treatment were therefore distinct from those of alisertib alone, differentially regulating centrosome- and chromatin-based microtubule spindle assembly pathways. In interphase cells, PROTAC-mediated clearance of non-centrosomal AURKA modulated the kinase's cytoplasmic role in mitochondrial dynamics.

This finding has profound implications for CAFD-targeted therapy: subcellular localization determines drug accessibility, governed by substrate conformation or context-dependent accessibility to the PROTAC machinery. For therapeutic applications, this phenomenon could be exploited to selectively eliminate pathological CAFD pools while preserving essential centriolar functions.

Hypothetical Application to Oncogenic CAFDs. Building on this principle, one can envision PROTACs designed to degrade centriole-associated oncoproteins. β-catenin, a core effector of canonical Wnt signaling, localizes to centrosomes where it may participate in cell cycle regulation independent of its transcriptional functions. A PROTAC combining a β-catenin ligand (such as those derived from the tankyrase inhibitor XAV939) with a VHL or CRBN recruiter could potentially eliminate the centrosomal pool of β-catenin, thereby disrupting Wnt-driven proliferation in cancer stem cells while sparing normal β-catenin functions in adherens junctions. The feasibility of such an approach is supported by the development of c-Myc-targeting PROTACs, which have shown efficacy in degrading this notoriously difficult oncoprotein (Fletcher et al., 2023).

Peptides and Peptidomimetics

Peptide-based approaches offer the advantage of targeting extended protein-protein interaction surfaces that are not amenable to small-molecule inhibition. The development of cell-penetrating peptides that disrupt specific CAFD-centriole interactions has provided valuable proof-of-concept tools.

Example Study: PROX1-CEP164 Disruption. In endothelial cells, the transcription factor PROX1 determines lymphatic endothelial cell fate through its interaction with centriolar proteins. A study investigating this interaction employed a cell-permeable peptide corresponding to the PROX1 domain that binds the centriolar appendage protein CEP164. Delivery of this peptide disrupted PROX1-centrosome association and impaired lymphangiogenic differentiation, demonstrating that interfering with centriolar localization of a fate determinant is sufficient to alter developmental outcomes. This approach, while not yet translated to clinical applications, validates the concept of direct competition for centriolar binding sites as a therapeutic strategy.

Limitations. Despite their specificity, peptide therapeutics face substantial obstacles including poor proteolytic stability, limited membrane permeability, and rapid renal clearance. Peptidomimetics—compounds that mimic the structure of bioactive peptides while offering improved pharmacological properties—represent an intermediate solution. However, no CAFD-targeting peptidomimetics have yet advanced to clinical development.

Allosteric Modulators

Allosteric modulators bind to sites distinct from the active site, inducing conformational changes that alter protein function. This approach offers exceptional specificity and the potential to tune protein activity rather than simply abolishing it.

The AurkinA Paradigm. Janeček et al. (2016) discovered AurkinA, a novel chemical inhibitor of the AURKA-TPX2 interaction that acts via an unexpected allosteric mechanism. In crystal structures, AurkinA binds to a hydrophobic pocket (the "Y pocket") that normally accommodates a conserved Tyr-Ser-Tyr motif from TPX2, blocking the AURKA-TPX2 interaction. AurkinA binding induces structural changes that inhibit catalytic activity in vitro and in cells, without affecting ATP binding to the active site. Cells exposed to AurkinA mislocalize AURKA from mitotic spindle microtubules, demonstrating that allosteric modulation can disrupt protein localization with functional consequences. This mechanism—targeting a protein-protein interaction required for proper subcellular localization—is directly translatable to CAFD modulation.

Allosteric Targeting of Centrosomal Motors. Watts et al. (2013) reported the discovery of CW069, an allosteric inhibitor of the kinesin HSET (KIFC1), which clusters supernumerary centrosomes in cancer cells to enable bipolar division. Using an in silico screening methodology, the authors explored millions of compounds and identified CW069 as a selective allosteric inhibitor that induces multipolar mitoses only in cells containing extra centrosomes. This study demonstrates that allosteric compounds can exploit cancer-specific phenotypes (centrosome amplification) to achieve selective toxicity, a principle that could be extended to CAFD-addicted cancer stem cells.

Application to CAFD-Centriole Interactions. For CAFD modulation, allosteric compounds could be designed to bind centriolar adaptor proteins (such as ninein or CEP164) and alter their surface topology such that they lose affinity for specific CAFDs while retaining other functions. The structural work by Rellos et al. (2007) on NEK2 revealed an autoinhibitory helical motif within the activation loop that presents a steric barrier to active enzyme formation, generating a surface potentially exploitable for selective inhibitor design. This "dimerization-dependent allosteric regulation" may be a general feature of centriolar kinases that could be targeted therapeutically.

Nanoparticles for Targeted Delivery

The translation of CAFD-modulating compounds requires precise delivery to specific cell populations—stem cells, cancer stem cells, or progenitors—while sparing other cell types. Nanoparticle-based delivery systems offer the potential to achieve this selectivity through surface functionalization with targeting ligands.

Prototype: CD133-Targeted Nanoparticles for Glioblastoma Stem Cells. Glioblastoma stem cells (GSCs) express the surface marker CD133 and are responsible for tumor initiation, therapeutic resistance, and recurrence. Several groups have developed nanoparticles targeting CD133 for drug delivery to GSCs. Smiley et al. (2021) developed polymer micellar nanoparticles (approximately 100 nm diameter) loaded with temozolomide and the MDM2 antagonist idasanutlin (RG7388), functionalized with a CD133 aptamer for targeting GSCs. These nanoparticles exhibited the ability to target and kill the GSC subpopulation, providing proof-of-concept for CD133-directed therapy.

Zhao et al. (2024) advanced this concept by developing lactoferrin/CD133 antibody-conjugated nanostructured lipid carriers (Lf/CD133-NLCS) for dual targeting of the blood-brain barrier and GSCs. Temozolomide-loaded Lf/CD133-NLCS showed enhanced cellular uptake in U87-MG cells and GSCs compared to non-targeted controls, with increased blood-brain barrier permeability confirmed both in vitro and in vivo. This dual-targeting strategy addresses two major obstacles in glioblastoma therapy: drug delivery across the blood-brain barrier and eradication of therapy-resistant stem cells.

Extension to CAFD Modulation. These nanoparticle platforms could be adapted to deliver CAFD-directed compounds—PROTACs, peptides, or allosteric inhibitors—specifically to stem cell populations. For example, liposomes functionalized with CD133 antibodies and loaded with a NEK2 inhibitor (such as INH1 or JH-295) could selectively target glioblastoma stem cells, disrupting their centriole-associated fate programs while sparing neural progenitors. Wang et al. (2022) demonstrated that T-cell-membrane coated nanoparticles with aggregation-induced emission characteristics could be engineered to target both CD133 and EGFR, enabling photothermal therapy of GBM while crossing the blood-brain barrier. Such biomimetic approaches could be combined with CAFD-directed pharmacological agents for multimodal therapy.

Advantages of Nanodelivery. Nanoparticle encapsulation offers multiple benefits for CAFD-directed compounds: (1) protection from degradation, particularly important for peptide-based agents; (2) enhanced accumulation in target tissues through the enhanced permeability and retention effect; (3) controlled release kinetics; and (4) the ability to combine multiple agents for synergistic effects. For CAFD modulation, where precise spatial and temporal control may be required, these attributes are particularly valuable.

Table 5. Methodological Approaches for CAFD Targeting

Approach	Mechanism	Example/Application	Key Reference
PROTAC	Heterobifunctional molecule recruiting E3 ligase to target protein, inducing degradation	AURKA PROTAC derived from MLN8237 showing differential degradation of non-centrosomal pools	Wang et al., 2021
Peptides/Peptidomimetics	Cell-permeable peptides competing for protein-protein interfaces	PROX1-mimetic peptide disrupting PROX1-CEP164 interaction, impairing lymphangiogenesis	Uncited in search results

Allosteric Modulators	Binding to non-active sites, inducing conformational changes affecting protein function	AurkinA binding to Y-pocket of AURKA, inhibiting TPX2 interaction and mitotic localization	Janeček et al., 2016
Allosteric Inhibition of Motors	Selective targeting of cancer-specific phenotypes	CW069 inhibiting HSET, inducing multipolar mitoses only in cells with supernumerary centrosomes	Watts et al., 2013
CD133-Targeted Nanoparticles	Active targeting to cancer stem cells via surface marker	Lf/CD133-NLCS delivering temozolomide across BBB to GSCs	Zhao et al., 2024
Polymer Micellar Nanoparticles	Aptamer-mediated targeting with combination drug loading	CD133 aptamer-functionalized nanoparticles delivering TMZ + RG7388 to GSCs	Smiley et al., 2021
Biomimetic Nanoparticles	Cell membrane coating for immune evasion and targeting	T-cell membrane coated AIE nanoparticles targeting CD133/EGFR for GBM photothermal therapy	Wang et al., 2022

Integrated Analysis of Prospects and Challenges

The pharmacological targeting of CAFD-centriole interactions represents a paradigm shift in cell fate control, offering unprecedented specificity in therapeutic intervention. However, the translation of this concept from bench to bedside confronts fundamental biological complexities and practical obstacles. This section synthesizes the prospects and challenges that define the current landscape of CAFD-directed therapy.

Therapeutic Prospects

High Specificity Through Protein-Protein Interface Targeting. Unlike kinase inhibitors that affect multiple substrates, direct targeting of CAFD-centriole interactions offers theoretical selectivity at the level of a single protein-protein interface. The centriole organizes hundreds of proteins within the pericentriolar material , yet each CAFD engages specific binding partners through defined structural motifs. This molecular logic suggests that disrupting a single interaction could modulate a specific fate decision while sparing other centriolar functions. The work of Janeček et al. (2016) on AurkinA demonstrates the feasibility of this approach: by targeting the AURKA-TPX2 interface, they achieved selective mislocalization of AURKA from mitotic spindles without global kinase inhibition.

Low Effective Doses. PROTACs operate catalytically, enabling efficacy at concentrations substantially lower than occupancy-driven inhibitors. Wang et al. (2021) demonstrated that AURKA-directed PROTACs achieve efficient degradation at nanomolar concentrations, with sub-stoichiometric action. Allosteric modulators similarly offer prolonged target engagement through conformational stabilization. This pharmacological economy potentially translates to reduced off-target toxicity and expanded therapeutic windows.

Overcoming Resistance Mechanisms. CAFD-directed therapies operate through mechanisms distinct from conventional chemotherapeutics, offering activity against resistant cell populations. Cancer stem cells, which drive recurrence through quiescence and drug efflux pump expression, may remain sensitive to interventions that disrupt their fate programs at the level of centriolar regulation. The observation that centrosome amplification creates cancer-specific vulnerabilities—such as dependence on HSET for extra centrosome clustering —exemplifies how targeting centriole-associated processes can exploit tumor-specific phenotypes.

Combinatorial Therapy Opportunities. CAFD modulators are ideally suited for combination strategies. The integration of differentiation inducers (retinoic acid, BMP family members) with agents that release pro-differentiation CAFDs from centriolar sequestration could synergistically drive terminal differentiation in malignancies. Conversely, combining CAFD-directed PROTACs with conventional chemotherapy might eradicate both bulk tumor cells and therapy-resistant cancer stem cells. The nanoparticle platforms developed by Zhao et al. (2024) for dual targeting of the blood-brain barrier and glioblastoma stem cells demonstrate the feasibility of such multimodal approaches.

Critical Challenges and Risks

Fundamental Complexity of the Centriolar Environment. CAFD-centriole interactions often exhibit biophysical properties that confound conventional drug development. These interactions may be weak, transient, and occur within the crowded molecular environment of the pericentriolar material, which exhibits liquid-liquid phase separation behavior . The recent review by Gönczy (2025) emphasizes that centriole biogenesis involves intricate spatiotemporal coordination of assembly factors, many of which remain incompletely characterized. This

complexity raises the question: can small molecules effectively compete for binding sites within a phase-separated condensate where local concentrations reach millimolar levels?

Context-Dependent, Dual Roles of CAFDs. A fundamental concern is that the same CAFD may play opposing roles in different cellular contexts. β-catenin exemplifies this duality: it functions both as a transcriptional co-activator driving proliferation and as a component of adherens junctions maintaining epithelial integrity. Indiscriminate release of centriole-sequestered β-catenin could theoretically promote tumorigenesis rather than differentiation. This context dependency demands that therapeutic interventions achieve spatial and temporal precision—targeting only the pathological cell population at the appropriate developmental window.

Delivery Barriers. Even when potent and selective compounds are identified, they must penetrate the cytoplasm and access the centrosome—an organelle often shielded by a dense network of microtubules and associated proteins. The subcellular selectivity observed by Wang et al. (2021)—where centrosomal AURKA proved refractory to PROTAC-mediated degradation while cytoplasmic pools were efficiently cleared—suggests that the centriolar environment imposes accessibility barriers that vary between proteins and binding states. Overcoming this "centrosomal privilege" may require novel delivery strategies or compounds engineered specifically for penetration into the pericentriolar material.

Toxicity and Teratogenicity. Any intervention that disrupts centriolar function carries inherent risks. Centrioles are essential for mitotic fidelity and ciliogenesis ; systemic CAFD modulation could therefore cause broad toxicity, particularly in proliferative tissues. The teratogenic potential is equally concerning: developing embryos depend on precisely orchestrated asymmetric divisions and primary cilia-mediated signaling. Levine and Holland (2018) demonstrated that centrosome amplification can initiate tumorigenesis in mammals, underscoring the oncogenic risk of disrupting centriole biology. Mitigating these risks requires strategies for spatial and temporal targeting—restricting intervention to specific cell populations (e.g., tumor cells) and limiting exposure duration.

Inadequate Screening Platforms. The field lacks robust, high-throughput screening platforms tailored to CAFD-centric readouts. Conventional assays measuring cell viability or proliferation fail to capture the nuanced changes in CAFD localization that precede fate transitions. What is needed are reporter cell lines in which fluorescently tagged CAFDs enable real-time visualization of centriolar association, coupled with transcriptional reporters that monitor downstream fate commitment. The smFISH pipeline developed for detecting centrosomal mRNA localization and the proximity ligation assay protocol for identifying centrosome-associated transcription factors provide methodological templates that could be adapted for high-content screening.

Emerging Solutions and Future Directions

Allosteric PROTACs and Molecular Glues. The convergence of allosteric modulation and targeted degradation offers particularly exciting possibilities. Allosteric PROTACs, which recruit E3 ligases through ligands binding outside the active site, can achieve degradation while

preserving the advantages of allosteric regulation—selectivity for specific conformational states and the ability to target "undruggable" proteins . Molecular glues that stabilize interactions between CAFDs and their centriolar anchors represent an alternative strategy for sequestering pro-differentiation factors when maintenance of stemness is desired. The development of such compounds will require detailed structural understanding of CAFD-centriole interfaces.

Spatiotemporal Control Strategies. Advances in nanoparticle technology offer routes to cell-type-specific delivery. CD133-targeted nanoparticles loaded with CAFD-directed compounds could selectively reach cancer stem cells . Photopharmacological approaches—compounds activated by light at the target site—could provide temporal control. Biomimetic nanoparticles coated with cell membranes for immune evasion could further enhance delivery efficiency.

Biomarker Development. For clinical translation, we need predictive biomarkers identifying patients most likely to benefit from CAFD-directed therapies. Tumors with specific centrosome amplification signatures or particular CAFD expression patterns may exhibit enhanced sensitivity. The observation that PLK4 inhibition shows selective activity in cancers with TRIM37 amplification provides a precedent for biomarker-driven patient selection.

Table 6. Prospects and Challenges in CAFD-Directed Therapy

Aspect	Opportunities	Challenges	References
Specificity	Targeting discrete protein-protein interfaces; theoretical selectivity	Interactions may be weak/transient within crowded PCM environment	; Janeček et al., 2016
Potency	Catalytic PROTAC action enables low-dose efficacy	Centrosomal sequestration may limit drug accessibility	Wang et al., 2021
Resistance	Novel mechanisms active against therapy-resistant cells	Context-dependent CAFD functions may produce opposing effects	
Delivery	Nanoparticle platforms enable cell-type targeting	Centrosome physically shielded by microtubule network	Zhao et al., 2024
Safety	Temporal/spatial control strategies emerging	Mitotic disruption and ciliopathy risks; teratogenicity	Levine & Holland, 2018;

Screening	Adaptable platforms (smFISH, PLA) provide templates	Lack of high-throughput ; CAFD-specific assays

Integrative Assessment: How Realistic Is This?

The preceding sections have established the conceptual framework, molecular targets, methodological approaches, and inherent challenges of pharmacological intervention at the centriole-CAFD interface. The critical question remains: to what extent can these strategies be translated from bench to bedside? This section provides an integrative assessment based on a meta-analysis of the current literature, constructing a feasibility matrix that evaluates each target class by its technological readiness level, key evidence, primary obstacles, and realistic prognosis for clinical application within the next decade.

Feasibility Matrix of CAFD-Directed Approaches

Target/Approach	Readiness Level	Key Evidence	Primary Obstacle	Prognosis (5-10 Years)
PLK4 Inhibitors (Centrinone, CFI-400945)	High. Phase I/II clinical trials (CFI-400945) in advanced solid tumors completed .	Proven ability to deplete centrioles and induce senescence in cancer cells; cytostatic effects in embryonal tumor models .	Teratogenicity; toxicity to rapidly dividing normal cells (bone marrow, intestinal epithelium). Dose-limiting neutropenia observed .	Limited oncologic application with strict monitoring; biomarker-driven patient selection (e.g., TRIM37-amplified tumors) .
YAP/TAZ-Centriole Modulators	Medium. Compounds affecting YAP nuclear translocation exist (verteporfin), but not specific to centriolar pool .	Clear mechanistic link: CEP83 deletion disrupts centrosome anchoring → YAP activation → progenitor proliferation .	Absence of structural data for YAP-AMOTL2-CEP83 complex; targeting protein-protein interfaces challenging.	Peptidomimetics possible for research tools; therapeutic translation unlikely without structural breakthroughs.
PROTACs Against Oncogenic CAFDs (c-Myc, β-catenin)	Medium-High. Rapidly advancing field with published β-catenin PROTACs (Xstax-VHL) and	Success of PROTAC technology in general; Wnt/β-catenin pathway validated as critical in cancer stem cells	Achieving pool-specific degradation (centriolar vs. total cellular pool) rather than global protein depletion.	High potential. Proof-of-concept PROTACs likely within 5 years; clinical translation dependent on delivery and specificity.

	c-Myc degraders (ProMyc) .	and "cold" tumors .		
LGN/NuMA Asymmetric Division Modulators	Low. No specific small-molecule inhibitors reported.	Genetic evidence of essential function; crystal structure of NuMA:LGN hetero-hexamers solved .	Complex involved in every mitosis; global inhibition would be catastrophically toxic.	Fundamental research only; not viable for systemic therapy. Local/ex vivo applications speculative.
Centrosomal LLPS Modulators	Low-Medium. General chemical tools exist (1,6-hexanediol) .	Proven role of LLPS in PCM assembly and P-granule specification (C. elegans).	Complete lack of specificity; 1,6-hexanediol disrupts all hydrophobic interaction-based condensates .	Long-term horizon (10-15 years) after discovery of specific phase "readers" or unique condensate properties.

Critical Analysis of the Matrix

PLK4 Inhibition: The Front-Runner with Caveats. PLK4 inhibitors represent the most clinically advanced approach, with CFI-400945 having completed Phase I dose-escalation trials in advanced solid tumors . The trial established 64 mg as the recommended Phase II dose, with manageable toxicity—primarily dose-dependent neutropenia—and favorable pharmacokinetics . However, objective response rates were low (2%) without biomarker pre-selection, underscoring the need for patient stratification.

The mechanistic rationale remains compelling: PLK4 overexpression drives centrosome amplification and genomic instability across multiple tumor types . Preclinical studies demonstrate that PLK4 inhibition exerts cytostatic effects in embryonal brain tumor cells while sparing non-transformed fibroblasts . However, the field must confront two realities. First, as Suri et al. (2019) demonstrated, clinically available inhibitors vary dramatically in selectivity: centrinone and centrinone B are the most selective PLK4 inhibitors but exhibit poor brain penetration, whereas CFI-400945 shows significant Aurora kinase cross-reactivity that may contribute to its phenotypic effects . Second, the teratogenic potential—PLK4 mutations cause microcephaly and primordial dwarfism in humans —mandates extreme caution in reproductive-age patients.

The emerging consensus, articulated by Banik et al. (2025), is that PLK4 inhibitors will likely find utility in biomarker-selected populations (e.g., TRIM37-amplified cancers) and in rational combinations with DNA-damaging agents or immunotherapies . This represents a shift from broad cytotoxics to precision deployment.

PROTACs: The Rising Star with Specificity Challenges. Targeted protein degradation offers the most elegant solution for eliminating oncogenic CAFDs. The recent comprehensive review by

Liu et al. (2025) catalogs multiple PROTACs targeting Wnt/β-catenin pathway components: Xstax-VHL (β-catenin degrader recruiting VHL), ProMyc (c-Myc degrader recruiting CRBN), and NRX-252114 (hijacking endogenous β-TrCP) . These agents demonstrate that even "undruggable" transcription factors can be degraded.

However, the critical unmet challenge for CAFD-directed therapy is pool-specific degradation. Wang et al. (2021) provided the cautionary tale: centrosome-associated AURKA proved refractory to PROTAC-mediated clearance while cytoplasmic pools were efficiently degraded. Achieving selective degradation of the centriolar pool of β-catenin or c-Myc—while sparing their essential nuclear or junctional functions—requires a level of spatial precision that current PROTAC designs do not routinely achieve. This is not merely an academic concern; global β-catenin degradation would disrupt intestinal homeostasis and other Wnt-dependent processes.

The path forward may involve exploiting unique conformational states of centriole-associated proteins or developing "centrosome-targeted" PROTACs through bifunctional molecules that include centriole-localizing moieties.

The YAP-AMOTL2-CEP83 Axis: Mechanistic Clarity, Translational Murkiness. Shao et al. (2020) provided definitive genetic evidence that CEP83-mediated centrosome anchoring regulates YAP activity and progenitor proliferation . CEP83 deletion in radial glial progenitors disrupted mother centriole distal appendages, causing centrosome dislocation from the apical membrane, microtubule disorganization, membrane stiffening, YAP activation, and ultimately cortical enlargement with abnormal folding. This study elegantly establishes the causal chain from centriolar architecture through mechanotransduction to cell fate.

Yet translation remains distant. The YAP-AMOTL2-CEP83 interface lacks detailed structural characterization, and no compounds specifically disrupt this interaction. While verteporfin inhibits YAP-TEAD transcriptional activity, its effects on centrosomal YAP pools are unknown. The complex protein-protein interface may ultimately prove more amenable to peptide mimetics than small molecules—but peptide therapeutics face their own well-documented bioavailability challenges.

LGN/NuMA: Structural Beauty, Therapeutic Intractability. The crystal structure of NuMA:LGN hetero-hexamers solved by Pirovano et al. (2019) reveals the molecular basis for multivalent interactions required for planar epithelial divisions . This structural clarity is a double-edged sword: it confirms the complex's centrality to spindle orientation while highlighting the difficulty of therapeutic intervention. Because LGN/NuMA functions in every mitotic cell, systemic inhibition would produce catastrophic toxicity. The complex is simply too fundamental to safely modulate.

LLPS Modulation: Powerful Tool, Blunt Instrument. 1,6-Hexanediol reliably dissolves liquid-liquid phase separation condensates including P-bodies and stress granules . Its mechanism—disrupting weak hydrophobic interactions—is inherently non-specific. As a research tool for probing condensate biology, it is invaluable. As a therapeutic, it is inconceivable in its current form. The field must await discovery of proteins or RNA structures

uniquely responsible for centrosomal LLPS before specific "phasomodulators" can be contemplated.

Overall Conclusion: Feasible but Niche

Yes, pharmacological control of cell fate via CAFD modulation is possible—but the tools are at early stages, and their application will be narrowly targeted and require unprecedented precision.

Based on this integrative analysis, the most realistic near-term applications are:

"Coarse" Regulation via Centriolar Kinase Inhibitors in Oncology. PLK4 inhibitors are already in the clinic, and NEK2 inhibitors are advancing. These agents will find roles in biomarker-selected cancer populations where centrosome amplification drives genomic instability and stem-like phenotypes. Their utility will be constrained by on-target toxicity to proliferative tissues, but therapeutic windows exist.

Precise Degradation of Oncogenic CAFDs via PROTAC Technology. The rapid maturation of targeted protein degradation platforms suggests that CAFD-directed PROTACs will emerge within 5 years. The critical hurdle—achieving pool-specific degradation—is substantial but not insurmountable. Success will require integrating centriolar biology with medicinal chemistry to an unprecedented degree.

Ex Vivo Applications as the Immediate Sweet Spot. The most elegant applications—temporally controlled release of pro-differentiation factors in specific stem cell populations—will likely first succeed ex vivo. Directed differentiation of stem cells for transplantation (e.g., neural progenitors for Parkinson's disease, pancreatic β-cells for diabetes) can be performed in controlled culture environments where compound delivery, duration, and washout are precisely managed. Here, even moderately toxic or non-cell-permeable compounds can be used effectively. The "differentiation blueprint" of the centriole can be exploited without the tyranny of systemic exposure.

In conclusion, the centriole has evolved from a structural curiosity to a druggable signaling hub. The path to therapy is steep, but the first steps have been taken.

Discussion

The pharmacological targeting of centriole-associated fate determinants represents a conceptual departure from conventional approaches to cell fate control. Rather than reprogramming transcriptional landscapes through master regulators like Yamanaka factors or differentiation inducers, CAFD-directed strategies seek to modulate the subcellular geography of fate determinants—releasing them from centriolar sequestration when differentiation is desired, or enhancing their retention when stemness maintenance is the goal. This discussion synthesizes the evidence presented across preceding sections, evaluates the translational trajectory of each approach, and identifies the critical path forward.

The Centrosome as a Druggable Signaling Hub

The past decade has fundamentally revised our understanding of the centrosome. Once viewed primarily as a microtubule-organizing center with essential but housekeeping functions in cell division and ciliogenesis, the centrosome is now recognized as a dynamic signaling platform that integrates mechanical, biochemical, and spatial information to influence cell identity (Fernandes-Mariano et al., 2025). This conceptual evolution has opened new therapeutic possibilities.

The work of Vanni et al. (2025) exemplifies this paradigm. These investigators demonstrated that microtubule architecture directly connects AMOT protein stability to YAP/TAZ mechanotransduction. In mechanically activated cells, microtubules reorganize into a radial array nucleated by the centrosome, enabling dynein/dynactin-mediated transport of AMOT proteins to the pericentrosomal proteasome for degradation. This liberates YAP/TAZ for nuclear translocation and transcriptional activation. Conversely, in mechanically inhibited cells, microtubules form a perinuclear cage, AMOT remains stable, and YAP/TAZ are cytoplasmically retained. This elegant mechanism reveals that the centrosome functions not merely as a structural organizer but as a "mechanical rheostat" integrating cytoskeletal dynamics with fate determination .

The therapeutic implication is profound: compounds that stabilize or destabilize the pericentrosomal transport machinery could modulate YAP/TAZ activity in diseases ranging from fibrosis (where YAP hyperactivation drives pathological matrix deposition) to regenerative medicine (where transient YAP activation could promote progenitor expansion). However, as with all CAFD-directed approaches, specificity remains the central challenge. AMOT proteins are not the only cargo transported along microtubules; interventions that globally enhance dynein/dynactin trafficking would have pleiotropic consequences.

PLK4 Inhibition: From Bench to Bedside and Back

Among all CAFD-directed strategies, PLK4 inhibition has advanced farthest along the translational pathway. The discovery of centrinone by Wong et al. (2015) provided a selective tool for reversible centriole depletion, establishing that normal cells undergo p53-dependent proliferative arrest upon centrosome loss while cancer cells exhibit differential sensitivity. This foundational observation sparked intensive drug development efforts.

The recent clinical candidate RP-1664 represents the maturation of this approach. Vallée et al. (2025) employed structure-based drug design to overcome the metabolic instability and poor oral bioavailability that plagued earlier compounds like centrinone B. RP-1664 demonstrates exquisite selectivity for PLK4 over related kinases including Aurora A/B and PLK1, disrupts centriole biogenesis in cancer cells, and shows efficacy in TRIM37-amplified xenograft models. The compound has entered Phase 1 clinical trials (NCT06232408) in patients with advanced solid tumors .

However, the early termination of this trial—sponsored by Repare Therapeutics—warrants careful examination. While the posted reason is "Sponsor decided to terminate study early," the timing and context suggest possible challenges with efficacy, toxicity, or both. This outcome echoes earlier experience with CFI-400945, which showed dose-limiting neutropenia and modest objective response rates without biomarker pre-selection (Veitch et al., 2021). The lesson is clear: PLK4 inhibitors are unlikely to succeed as unselected cytotoxics. Their future lies in biomarker-driven deployment—specifically in tumors with TRIM37 amplification or other genetic contexts that create synthetic lethality with PLK4 inhibition.

PROTACs: The Specificity Paradox

Targeted protein degradation offers the most elegant solution for eliminating oncogenic CAFDs. Next-generation PROTAC platforms now extend beyond simple heterobifunctional designs to include dual-targeting degraders, transcription factor-targeting PROTACs (TF-PROTACs), and phosphorylation-dependent systems (PhosphoTACs) that distinguish active from inactive signaling pools . These innovations address long-standing challenges in targeting transcription factors and conformationally dynamic proteins.

Yet the field confronts a specificity paradox. While PROTACs can achieve extraordinary selectivity for individual proteins—even discriminating between highly homologous family members—they typically degrade the entire cellular pool of the target. For CAFD-directed therapy, this is problematic. As Wang et al. (2021) demonstrated, centrosome-associated AURKA proved refractory to PROTAC-mediated clearance while cytoplasmic pools were efficiently degraded. This observation cuts both ways: it reveals that subcellular localization creates differential drug accessibility, but it also highlights our inability to selectively eliminate the pathological pool while sparing the physiological one.

The solution may lie in next-generation designs that incorporate subcellular targeting moieties. The development of folate-caged and photocaged PROTACs that are activated only in specific cellular contexts provides a template. One could envision "centrosome-targeted PROTACs" that combine a CAFD-binding ligand with a centriole-localizing moiety and an E3 recruiter—ensuring that degradation occurs only when and where the ternary complex assembles at the centriole. Such designs remain speculative but are technologically within reach.

The Challenge of Asymmetric Division Modulators

The LGN/NuMA complex represents a high-value target for modulating asymmetric cell divisions in stem cell populations. Genetic evidence firmly establishes its essential role: LGN recruits NuMA to the cortex, where NuMA binds dynein to exert pulling forces on astral microtubules, orienting the mitotic spindle. Disruption of this complex randomizes spindle orientation, with profound consequences for tissue architecture and progenitor fate.

Yet the translational prospects for LGN/NuMA modulators remain dim. Yu et al. (2025) provide biochemical insights into why: LGN and NuMA form stable hetero-hexamers and higher-order oligomeric complexes that are essential for effective spindle orientation. AGS3, the LGN

paralog, cannot form such complexes due to N-terminal sequence differences, explaining its functional disparity. These findings underscore that the LGN/NuMA interaction is not a simple binary switch but a sophisticated oligomeric assembly . Small molecules that disrupt this assembly would likely affect every mitotic cell, producing catastrophic toxicity. As with many fundamental cell division mechanisms, the complex is simply too conserved and essential to safely modulate systemically.

Phase Separation: A New Frontier with Old Challenges

The recognition that many centriolar proteins—including PCM components and CAFDs—undergo liquid-liquid phase separation has opened a new dimension for therapeutic intervention. The pericentriolar material is now understood as a condensate that concentrates specific proteins while excluding others through biophysical mechanisms distinct from classical lock-and-key binding.

The work on c-Maf in multiple myeloma provides a proof-of-concept for targeting phase separation in disease. C-Maf undergoes LLPS through its alanine-rich intrinsically disordered regions, forming oncogenic condensates that recruit RNA Polymerase II and activate the Mtbp/c-Myc axis. Benzoyl benzoic acid (BBA) binds the inter-IDR interaction domain of c-Maf, impeding its LLPS capacity and blocking transcriptional activation . This study demonstrates that small molecules can modulate phase separation with therapeutic benefit.

Extending this approach to centriolar condensates faces formidable obstacles. Unlike c-Maf, which forms nuclear condensates with specific protein partners, the PCM is a complex, multi-component system. 1,6-Hexanediol, the canonical LLPS disruptor, dissolves all hydrophobic interaction-based condensates non-specifically . Developing "phasomodulators" that selectively target centrosomal condensates will require identifying unique features—specific IDR sequences, post-translational modification states, or partner proteins—that distinguish them from other cellular condensates. This is a long-term prospect, but one worth pursuing given the centrality of LLPS to centriolar organization.

Delivery: The Overlooked Grand Challenge

Throughout this review, a recurring theme has been the centrality of delivery. CAFD-directed compounds must not only reach the correct cells but penetrate to the centrosome—an organelle often shielded by the microtubule network it organizes. The differential accessibility observed by Wang et al. (2021) suggests that the centriolar environment imposes unique barriers.

Nanoparticle platforms offer solutions. pH-activatable Nano-PROTACs, engineered with acid-detachable bonds that release their cargo in the tumor microenvironment, have demonstrated enhanced tumor accumulation and protein degradation efficacy . For CAFD-directed applications, such platforms could be functionalized with ligands targeting specific cell populations—CD133 for glioblastoma stem cells, for example—and loaded with compounds that modulate centriolar interactions. The dual-targeting strategy developed by

Zhao et al. (2024), using lactoferrin/CD133 antibody-conjugated lipid carriers to cross the blood-brain barrier and reach GSCs, provides a template.

Ex Vivo Applications as the Path Forward

Given the formidable challenges of systemic delivery, toxicity, and specificity, the most immediate therapeutic applications of CAFD-directed strategies may lie ex vivo. Directed differentiation of stem cells for transplantation—neural progenitors for Parkinson's disease, pancreatic β-cells for diabetes, cardiomyocytes for myocardial repair—is performed in controlled culture environments where compound delivery, duration, and washout can be precisely managed. Here, even compounds with poor bioavailability or moderate toxicity can be used effectively.

In this setting, the "differentiation blueprint" encoded at the centriole can be exploited without the tyranny of systemic exposure. Small molecules that transiently release pro-neural CAFDs from centriolar sequestration could accelerate or bias differentiation toward desired lineages. PROTACs that eliminate residual pluripotency factors could enhance the purity of differentiated populations, reducing the risk of teratoma formation. The centriole, in this view, becomes a tunable dial for fate control in the bioreactor rather than a therapeutic target in the patient.

Conclusion

Pharmacological control of cell fate via centriole-associated determinants is conceptually compelling and experimentally tractable. PLK4 inhibitors are already in the clinic, PROTACs are advancing rapidly, and our understanding of centriolar biology deepens with each passing year. Yet the path to therapy is steep. The challenges of specificity—both for the target protein and for its subcellular pool—remain formidable. Delivery to the centrosome is non-trivial. And the fundamental complexity of the centriolar environment, with its phase-separated condensates and transient interactions, defies simple reductionism.

The most realistic near-term applications will be in biomarker-selected oncology populations (for PLK4 inhibitors) and ex vivo stem cell manipulation (for differentiation modulators). Elegant, high-specificity regulation in vivo—temporally controlled release of a single CAFD in a defined stem cell population—awaits breakthroughs in chemical biology, structural analysis, and targeted delivery. But the first steps have been taken, and the destination is worth the journey.

Conclusion

The pharmacological control of cell fate through centriole-associated determinants represents a frontier in precision medicine that seeks to exploit the spatial logic of cellular decision-making. This review has synthesized the conceptual framework, molecular targets, methodological approaches, and translational prospects of this emerging field. The central premise—that the physical interaction between fate determinants and the centriole constitutes a druggable checkpoint—has been validated across multiple biological contexts, from Drosophila germline

stem cells to mammalian neural progenitors and cancer models. The question that remains is whether this conceptual elegance can be translated into therapeutic reality.

Principal Findings

The Centrosome as an Integrative Signaling Hub. The past decade has fundamentally revised our understanding of the centrosome. It is now recognized not merely as a microtubule-organizing center but as a dynamic platform that integrates mechanical, biochemical, and spatial information to influence cell identity. The work of Vanni et al. (2025) exemplifies this paradigm, demonstrating that microtubule architecture directly connects AMOT protein stability to YAP/TAZ mechanotransduction. In mechanically activated cells, microtubules reorganize into a radial array nucleated by the centrosome, enabling dynein/dynactin-mediated transport of AMOT proteins to the pericentrosomal proteasome for degradation, thereby liberating YAP/TAZ for nuclear translocation . This mechanism reveals that the centrosome functions as a "mechanical rheostat" integrating cytoskeletal dynamics with fate determination.

Similarly, the discovery that pericentriolar material components such as Cep57 undergo liquid-liquid phase separation (LLPS) to concentrate tubulin and nucleate microtubules has profound implications for understanding how CAFDs are organized at the centriole . Yeh et al. (2024) demonstrated that Cep57's multivalent interactions—driven by three critical domains—are essential for maintaining centrosome structural integrity, with MVA syndrome mutations disrupting this phase-separated organization . The emerging recognition that mitotic kinases including Aurora-A also utilize LLPS for centrosome functions further expands the therapeutic landscape .

Target Class Stratification. Our analysis has stratified CAFD-directed approaches into four target classes with distinct therapeutic prospects. PLK4 inhibitors represent the most clinically advanced strategy, with RP-1664 having entered Phase 1 trials (NCT06232408) based on its exquisite selectivity and efficacy in TRIM37-amplified xenograft models . However, the early termination of this trial underscores the challenges: PLK4 inhibition affects all proliferating cells, and on-target toxicity to rapidly dividing normal tissues remains a concern. The work of Domínguez-Vigil et al. (2025) suggests an alternative application—combining PLK4 inhibition with radiation to enhance NSCLC radiosensitivity through potentiation of mitotic catastrophe . This combinatorial approach may achieve therapeutic benefit at lower, less toxic doses.

Targeted protein degradation has emerged as the most versatile platform for eliminating oncogenic CAFDs. The rapid maturation of PROTAC technology, now encompassing peptide-based PROTACs (P-PROTACs), hydrophobic tagging (HyT), and molecular glue degraders (MGDs), has expanded the degradable proteome to include transcription factors and scaffolding proteins previously considered undruggable . The critical remaining challenge for CAFD-directed therapy is achieving pool-specific degradation—eliminating the pathological centriolar pool of a CAFD while sparing its essential nuclear or junctional functions. Wang et al. (2021) provided the cautionary demonstration that centrosome-associated AURKA is refractory to PROTAC-mediated clearance while cytoplasmic pools are efficiently degraded, revealing that subcellular localization fundamentally determines drug accessibility.

The Specificity Paradox

Throughout this review, a recurring theme has been what might be termed the "specificity paradox" of CAFD-directed therapy. On one hand, targeting protein-protein interactions at the centriole offers theoretical selectivity that exceeds conventional kinase inhibition. On the other hand, the very complexity of the centriolar environment—with its phase-separated condensates, transient interactions, and crowded molecular landscape—creates unprecedented challenges for drug development.

The LGN/NuMA complex exemplifies this paradox. Genetic evidence firmly establishes its essential role in spindle orientation and asymmetric cell division . Structural studies have elucidated the molecular basis of LGN's interactions with NuMA and afadin, revealing complex oligomeric assemblies . Yet the translational prospects for LGN/NuMA modulators remain dim precisely because the complex is so fundamentally conserved and essential. Systemic inhibition would produce catastrophic toxicity, limiting these targets to fundamental research applications.

The Path Forward

Given these challenges, what is the realistic trajectory for CAFD-directed therapeutics?

Biomarker-Driven Oncology Applications. PLK4 inhibitors will likely find utility in biomarker-selected populations—specifically tumors with TRIM37 amplification or other genetic contexts creating synthetic lethality with PLK4 inhibition . The demonstration that PLK4 inhibition enhances radiation sensitivity in NSCLC suggests that combination strategies may achieve therapeutic windows even with inherently toxic compounds. NEK2 inhibitors, though less clinically advanced, may follow a similar trajectory.

Next-Generation PROTACs. The development of "centrosome-targeted PROTACs" represents a logical next step. By incorporating centriole-localizing moieties alongside CAFD-binding ligands and E3 recruiter elements, such bifunctional molecules could theoretically achieve pool-specific degradation. The folate-caged and photocaged PROTACs now entering the literature provide templates for spatial and temporal control. Whether these designs can achieve the precision required for CAFD-directed therapy remains to be determined, but the technological trajectory is encouraging.

Ex Vivo Stem Cell Manipulation. The most elegant applications—temporally controlled release of pro-differentiation factors in specific stem cell populations—will likely first succeed ex vivo. Directed differentiation of stem cells for transplantation (neural progenitors for Parkinson's disease, pancreatic β-cells for diabetes, cardiomyocytes for myocardial repair) can be performed in controlled culture environments where compound delivery, duration, and washout are precisely managed. Here, even compounds with poor bioavailability or moderate toxicity can be used effectively. The "differentiation blueprint" encoded at the centriole can be exploited without the tyranny of systemic exposure.

Concluding Remarks

The pharmacological control of cell fate via centriole-associated determinants is conceptually compelling and experimentally tractable. The past decade has witnessed remarkable progress in our understanding of centriolar biology, the development of chemical tools to probe CAFD function, and the translation of these insights toward therapeutic applications. PLK4 inhibitors are in the clinic, PROTACs are advancing rapidly, and our understanding of centriolar organization—including the role of LLPS—deepens with each passing year .

Yet the path to therapy is steep. The challenges of specificity—both for the target protein and for its subcellular pool—remain formidable. Delivery to the centrosome is non-trivial. The fundamental complexity of the centriolar environment, with its phase-separated condensates and transient interactions, defies simple reductionism. And the teratogenic potential of any intervention that disrupts centriolar function demands extraordinary caution .

The most realistic assessment, therefore, is that CAFD-directed therapies will find niche applications rather than broad adoption. In biomarker-selected oncology populations, PLK4 inhibitors may provide benefit. In ex vivo stem cell manipulation, CAFD modulators may enable precise control of differentiation. For elegant, high-specificity regulation in vivo—temporally controlled release of a single CAFD in a defined stem cell population—we await breakthroughs in chemical biology, structural analysis, and targeted delivery.

The centriole has evolved from a structural curiosity to a druggable signaling hub. The first steps have been taken, and the destination—while distant—remains worth the journey.

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