

Why do planarian cells without centrioles divide and cells with centrioles do not divide?

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Abstract

Planarians present a unique cellular paradox: their proliferative stem cells (neoblasts) completely lack centrioles, while their post-mitotic, differentiated cells possess them. This review investigates the mechanisms and biological significance of this inverse correlation. We synthesize evidence demonstrating that neoblasts employ a robust, evolutionarily conserved acentrosomal pathway for spindle assembly, reliant on chromatin-mediated nucleation via RanGTP and motor protein-driven self-organization. This adaptation potentially confers advantages including enforced asymmetric division, metabolic economy, and a significantly reduced risk of centrosome amplification-driven genomic instability, which may underpin the planarians' extensive regenerative capabilities and resistance to tumors. Conversely, the quiescence of centriole-bearing somatic cells is not caused by the organelles themselves but is a consequence of terminal differentiation. These cells epigenetically silence the cell cycle machinery and repurpose centrioles as basal bodies for ciliogenesis. The presence of centrioles is thus a marker, not a driver, of the differentiated state. This system represents a profound uncoupling of the mitotic apparatus from the centriole, offering novel insights into stem cell biology, alternative modes of cell division, and providing conceptual frameworks for regenerative medicine and cancer research.

Keywords: Planarian, Neoblast, Centriole, Acentrosomal Spindle Assembly, Regeneration, Stem Cell, Differentiation, Chromosomal Instability, Asymmetric Cell Division.

Introduction: The Planarian as a Unique Model for Regeneration and Stem Cell Biology

The quest to understand the fundamental principles of tissue regeneration and stem cell biology has led researchers to explore a diverse array of model organisms. Among these, planarians (free-living flatworms of the order Tricladida) stand out due to their phenomenal regenerative capabilities, which have fascinated scientists for centuries (Reddien, 2018). A single fragment of the planarian body, representing as little as 1/279th of the original organism, can regenerate a complete, perfectly proportioned animal within a matter of weeks (Newmark & Sánchez Alvarado, 2002). This remarkable process is not driven by a limited wound-healing response but by the activation of a ubiquitous and potent population of adult somatic stem cells, known collectively as neoblasts (Wagner et al., 2011). The molecular and cellular machinery underpinning planarian regeneration offers profound insights into the control of cell proliferation, differentiation, and patterning, making them a powerful model for biomedical research (Gentile et al., 2011).

The species *Schmidtea mediterranea*, in particular, has emerged as a premier model system due to its diploid chromosomes and the development of robust genetic tools, including RNA interference (RNAi) and next-generation sequencing methodologies (Reddien et al., 2005; Zayas et al., 2005). The regenerative prowess of *S. mediterranea* is entirely dependent on neoblasts. These cells are the only proliferative cells in the adult planarian body and are responsible for both homeostatic tissue turnover and the massive blastema formation required for regeneration (van Wolfswinkel et al., 2014). Ablation of neoblasts, for instance through irradiation, completely abolishes regeneration and leads to the eventual death of the animal, unequivocally demonstrating their status as the engine of renewal (Elliott & Sánchez Alvarado, 2013).

A deep paradox lies at the heart of the planarian stem cell system, presenting a fascinating challenge to conventional cell biological dogma. Neoblasts, which are mitotically active and must faithfully segregate their genome during every division, remarkably lack centrioles (Azimzadeh et al., 2012). In the vast majority of animal cells, centrioles are essential microtubule-organizing centers (MTOCs) that form the core of the centrosome and are crucial for assembling the bipolar mitotic spindle, ensuring accurate chromosome segregation (Conduit et al., 2015). The absence of these canonical organelles in the primary stem cell of such a complex organism is, therefore, both striking and counterintuitive. Studies have confirmed that neoblasts undergo an acentrosomal mitosis, assembling their mitotic spindles via a mechanism that likely relies on chromatin-mediated microtubule nucleation and stabilization by motor proteins (Müller-Reichert et al., 2022). This places planarian neoblasts in a rare category of cells capable of robust, acentriolar cell division, a feat typically associated with the female meiosis of many animals and the early embryonic divisions of some species (Dumont & Desai, 2012).

This stands in stark contrast to the other cell types within the planarian body. Differentiated cells, such as neurons, pharyngeal cells, and the ciliated cells of the ventral epidermis, possess fully

formed centrioles, which in these post-mitotic cells function primarily as basal bodies to nucleate cilia (Rink et al., 2009; Gonzalez-Sastre et al., 2017). Despite housing the very organelles considered quintessential for cell division, these differentiated cells are entirely incapable of proliferation. They exist in a permanent state of quiescence (G0 phase), and their centrioles are never recruited to organize a mitotic spindle (Pearson & Sánchez Alvarado, 2010). This creates a clear and puzzling inverse correlation: the cells without centrioles (neoblasts) are proliferative, while the cells with centrioles (somatic cells) are post-mitotic.

This fundamental dichotomy raises critical questions about the regulation of the cell cycle and the very role of centrioles in stem cell biology. Why have planarian stem cells evolutionarily discarded a structure so central to cell division in other metazoans? Does the absence of centrioles confer a specific advantage to neoblasts, perhaps related to their stemness, their mode of division (symmetric vs. asymmetric), or the prevention of aberrant proliferation? Conversely, does the presence of a centriole in a differentiated cell act merely as a passive marker of a terminal state, or could it play a more active role in enforcing post-mitotic arrest by repressing cell cycle re-entry?

The primary goal of this article is to investigate this cellular paradox. We will synthesize current evidence to explore the molecular and cellular mechanisms that enable acentriolar neoblasts to successfully proliferate with high fidelity. Furthermore, we will examine the potential reasons why the presence of centrioles in differentiated planarian cells correlates with, and may even contribute to, their irreversible exit from the cell cycle. Resolving this paradox is not only essential for a complete understanding of planarian biology but also provides broader insights into alternative mechanisms of cell division and the intricate relationship between cellular architecture and cell fate determination.

Centrioles and the Mitotic Spindle: The Canonical Pathway of Mitosis

The faithful transmission of genetic material during cell division is a fundamental process in eukaryotic life, orchestrated by a complex macromolecular machine known as the mitotic spindle. For over a century, the centrosome, an organelle comprised of a pair of centrioles surrounded by pericentriolar material (PCM), has been established as the primary microtubule-organizing center (MTOC) responsible for assembling this spindle in animal cells (Conduit et al., 2015). The centrioles themselves, nine-fold symmetric barrel-shaped structures, act as the foundational core that recruits the PCM, a protein-dense matrix that nucleates and anchors microtubules (Woodruff et al., 2014). The function of centrioles, therefore, extends beyond mere structural elements; they are the central architects of the cytoskeletal landscape during mitosis.

The canonical pathway of mitotic spindle assembly is a centrosome-centric process. During interphase, the centrosome duplicates, and the two resultant centrosomes migrate to opposite poles of the nuclear envelope as mitosis commences (Nigg & Holland, 2018). Following nuclear

envelope breakdown, each centrosome nucleates a radial array of dynamic microtubules, forming an aster. These microtubules explore the cytoplasm, and through a combination of motor protein activity and microtubule-microtubule interactions, they self-organize into a bipolar, fusiform mitotic spindle (Prosser & Pelletier, 2017). The kinetochores on chromosomes capture microtubules from both poles, establishing bi-orientation and tension, which is the prerequisite for the anaphase separation of sister chromatids (Musacchio & Desai, 2017). The centrosomes, positioned at the spindle poles, provide structural stability and ensure the geometric fidelity of this process, guaranteeing that chromosome segregation is both accurate and symmetric.

The presence of centrioles as the organizing core of centrosomes is considered the gold standard for ensuring orderly and precise mitosis across most metazoan cell types. Their role is so critical that their dysfunction is intimately linked to severe cellular pathologies. Numerical or structural aberrations in centrioles can lead to the formation of multipolar spindles, merotelic attachments (where a single kinetochore is attached to both poles), and subsequent mitotic delays or errors in chromosome segregation (Godinho & Pellman, 2014). This genomic instability, manifesting as aneuploidy (an abnormal number of chromosomes), is a hallmark of cancer cells and a driving force in tumorigenesis (Levine & Holland, 2018). Furthermore, mutations in genes encoding centrosomal proteins are associated with a spectrum of human diseases, collectively known as "centrosomopathies," which include microcephaly, ciliopathies, and certain cancers (Nigg & Raff, 2009). The evidence is overwhelming: in the vast majority of documented cases, proper centriole function is non-negotiable for error-free cell division.

This established dogma, however, is powerfully challenged by the existence of planarian neoblasts. These cells represent a profound exception to the rule, demonstrating that precise and prolific mitosis can occur via an alternative, acentriolar pathway. Neoblasts completely lack centrioles, as confirmed ultrastructurally and by the absence of key centriolar markers (Azimzadeh et al., 2012). This observation immediately poses a fundamental problem: how do these cells assemble a functional bipolar spindle without the central organizers that are deemed essential? The neoblast system forces a re-evaluation of the absolute requirement for centrioles in mitosis and suggests that alternative, evolutionarily conserved mechanisms of spindle assembly can be sufficient, and perhaps even preferentially employed, in certain stem cell contexts.

The planarian paradox thus creates a clear dichotomy that sits at the intersection of cell biology and stem cell research. On one hand, we have the canonical model, where centriole-based spindle assembly is the norm, and its failure leads to disease. On the other hand, we have planarian neoblasts, which proliferate successfully for the lifetime of the animal using a non-canonical pathway, all while their differentiated progeny, which possess centrioles, are permanently barred from division. This stark contrast moves the scientific inquiry from a simple observation of an exception to a series of mechanistic questions: What molecular pathways substitute for the centrosomal function in neoblasts? Is the acentrosomal mode of division more prone to error, and if not, what safeguards ensure its fidelity? And ultimately, does the absence of centrioles confer a specific biological advantage to the neoblast state, potentially relating to its stemness or its role in regeneration? Addressing these questions is crucial to understanding

the full spectrum of mechanisms that eukaryotic cells employ to accomplish the critical task of division.

Cellular Heterogeneity in Planarians: Neoblasts vs. Differentiated Cells

The planarian body plan, while seemingly simple, is a complex mosaic of cell types that exhibit a stark functional dichotomy. This cellular heterogeneity is fundamental to understanding the organism's regenerative capabilities and is central to the paradox of centriole-bearing and centriole-lacking cells. The adult planarian soma is composed of two broad, functionally antagonistic categories: a single population of pluripotent, proliferative stem cells (neoblasts) and a diverse array of terminally differentiated, post-mitotic cells. This chapter will define these populations based on their morphological characteristics, molecular markers, and most importantly, their relationship with the centriole and the cell cycle.

Neoblasts: The Acentriolar Proliferative Engine

Neoblasts are the cornerstone of planarian biology. They are small (~5-10 μm in diameter), undifferentiated cells characterized by a high nuclear-to-cytoplasmic ratio, a large, ovoid nucleus with diffuse chromatin, and scant cytoplasm that is rich in ribosomes (Cowles et al., 2013; Zhu et al., 2015). This morphology is classically associated with stem and progenitor cells across metazoans, reflecting a state primed for gene expression and protein synthesis in service of proliferation and differentiation.

The definitive molecular signature of planarian neoblasts is the expression of genes from the piwi family. Piwi genes encode Argonaute-family proteins that are strongly conserved markers for germline and somatic stem cells in many organisms (Juliano et al., 2011). In *Schmidtea mediterranea*, the protein product of the gene **smedwi-1** (*Schmidtea mediterranea piwi-1*) is the most widely used marker for identifying neoblasts (Reddien et al., 2005). Immunostaining with anti-Smedwi-1 antibodies reveals a vast population of small, scattered cells throughout the parenchyma, excluding the organ structures and the region anterior to the photoreceptors. The expression of piwi genes is not merely correlative; it is functionally essential for neoblast maintenance and regeneration, as RNAi-mediated knockdown of **smedwi-1** leads to the loss of neoblasts, failure to regenerate, and animal death (Reddien et al., 2005).

The most remarkable and defining ultrastructural feature of neoblasts, in the context of this study, is their complete lack of centrioles. This was conclusively demonstrated through transmission electron microscopy (TEM), which failed to identify any centriolar structures in these cells despite their active division (Azimzadeh et al., 2012). This morphological evidence is strongly supported by molecular data: neoblasts show no expression of core centriolar components. For instance, γ -tubulin, a critical protein found in the pericentriolar material required for microtubule nucleation in centrosomes, is not localized to discrete puncta in dividing neoblasts, unlike in canonical centrosome-driven mitosis (Azimzadeh et al., 2012). Furthermore,

transcriptomic analyses of FACS-sorted neoblasts show low or absent expression of mRNAs encoding other centriole components like SAS-4/CPAP, SAS-6, and PLK4 (Labbe et al., 2012; Wagner et al., 2012). Thus, neoblasts are not merely cells that can sometimes divide without centrioles; they are fundamentally acentriolar cells that have evolutionarily lost the entire machinery for centriole biogenesis.

Differentiated Cells: The Centriolar Post-Mitotic Tissues

In stark contrast to the neoblasts, all other cells in the planarian body are terminally differentiated and form the functional tissues and organs of the animal. This includes a wide variety of cell types such as neurons (of which there are over 30 subtypes), multiciliated cells of the protonephridia and epidermis, secretory cells of the intestine, muscle cells, and various types of gland cells (Witchley et al., 2013; Plass et al., 2018). These cells are defined by their specialized morphology, which is tailored to their function—neurons extend long axons, epidermal cells develop numerous cilia, and gut cells form a branched lumen.

Critically, these differentiated cells possess fully formed, canonical centrioles. In ciliated cell types, such as the epidermal cells that cover the entire ventral surface of the animal, centrioles are present in large numbers as basal bodies, which nucleate the assembly of motile cilia essential for locomotion (Rink et al., 2009; Gonzalez-Sastre et al., 2017). Even in non-ciliated cell types like neurons, centrioles are present, though their function may be related to microtubule organization or other, less understood roles (Ahmad & Baas, 1995). The presence of centrioles in these cells is easily demonstrable through immunofluorescence staining for markers like γ -tubulin or centrin, which reveal clear, punctate signals at the base of cilia in epidermal cells (Azimzadeh et al., 2012).

The defining functional characteristic of these centriole-bearing cells is their absolute and permanent exit from the cell cycle. They reside in a state of deep quiescence (G0 phase) and never re-enter the mitotic cycle (Pearson & Sánchez Alvarado, 2010). This post-mitotic state is enforced by robust molecular mechanisms. Differentiated cells downregulate the expression of core cell cycle regulators, such as cyclins and cyclin-dependent kinases (CDKs), and activate pathways that maintain terminal differentiation (Onal et al., 2012). Attempts to force cell cycle re-entry in these cells, for example through oncogene expression, are typically unsuccessful and often lead to cell death rather than division, a safeguard that is crucial for the stability of a long-lived organism (Pearson & Sánchez Alvarado, 2010).

This clear cellular dichotomy establishes the central paradox: the proliferative unit of the planarian is defined by the absence of the organelle traditionally required for proliferation (the centriole), while the non-dividing somatic tissues are defined by its presence. This inverse relationship suggests that the presence or absence of a centriole is not a random occurrence but is intrinsically linked to the cellular identity and proliferative fate of the cell. Understanding how neoblasts achieve division without centrioles and why the possession of a centriole is synonymous with a post-mitotic state in planarians is key to unraveling this unique biological strategy.

The Mechanism of Acentriolar Division in Neoblasts

The absence of centrioles in planarian neoblasts necessitates an alternative, non-canonical pathway for assembling the mitotic spindle. This acentrosomal mechanism must fulfill the same critical functions as its centrosomal counterpart: it must efficiently nucleate microtubules, organize them into a bipolar array, and facilitate the correct attachment and segregation of chromosomes. Research over the past decade has begun to unravel the molecular players and physical principles that govern this remarkable process in neoblasts, revealing a strategy that is both sophisticated and evolutionarily ancient.

The Acentrosomal Pathway of Spindle Assembly

Neoblasts entirely bypass the centrosome-dependent pathway for initiating spindle formation. Instead of relying on predefined MTOCs at discrete poles, they employ a decentralized mechanism where spindle assembly is driven by the chromosomes themselves and the self-organizing properties of microtubules and associated motor proteins (Müller-Reichert et al., 2022). This strategy is not a peculiarity of planarians but represents one of the two fundamental modes of spindle formation in eukaryotes, the other being the centrosomal pathway (Dumont & Desai, 2012). In the absence of centrioles, the cytoplasm of the dividing neoblast becomes the stage for a search-and-capture process that is initiated from multiple sites within the cell.

The Central Role of Chromosomes: The RanGTP Pathway

The primary nucleating signal for acentrosomal spindle assembly emanates from the chromosomes. A key regulator in this process is the small GTPase Ran. Around the chromosomes, the guanine nucleotide exchange factor RCC1, which is bound to chromatin, generates a high local concentration of Ran in its GTP-bound form (RanGTP) (Clarke & Zhang, 2008). This RanGTP gradient acts as a spatial cue that propagates the influence of the chromosomes into the surrounding cytoplasm. RanGTP promotes the release and activation of specific spindle assembly factors (SAFs) from importin proteins that keep them inactive during interphase (Caudron et al., 2005). These activated SAFs include proteins that stabilize microtubules, nucleate new microtubules, and regulate motor protein activity. Consequently, this RanGTP-dependent mechanism leads to the intensive nucleation of new microtubules directly in the vicinity of the chromosomes, effectively creating a microtubule cloud that ensheathes the condensing chromatin (Meunier & Vernos, 2012). This chromatin-mediated nucleation is a cornerstone of acentrosomal spindle assembly and is believed to be the primary mechanism initiating spindle formation in neoblasts.

Self-Organization of Microtubules and Motor Protein Activity

The initial cloud of randomly oriented microtubules generated around the chromosomes is inherently unstable and must be structured into a stable, bipolar spindle. This organization is achieved through the coordinated action of motor proteins, which crosslink and slide microtubules relative to one another. Two classes of motor proteins are particularly crucial:

plus-end-directed homotetrameric kinesins (e.g., kinesin-5/Eg5) and minus-end-directed cytoplasmic dynein (Burbank et al., 2007; Tanenbaum et al., 2008).

Kinesin-5 motors, which crosslink adjacent microtubules and push them apart, are essential for establishing and maintaining spindle bipolarity. Inhibition of kinesin-5 in acentrosomal systems often leads to the collapse of the bipolar spindle into a monopolar array (Mountain et al., 1999). Conversely, cytoplasmic dynein plays a critical role in focusing the minus ends of microtubules to form spindle poles. Dynein, often in complex with its cofactors dynactin and NuMA, can tether the minus ends of microtubules and pull them together, effectively clustering them into defined poles even in the absence of centrosomes (Merdes et al., 1996; Gaglio et al., 1996). The antagonistic forces generated by these opposing motors—kinesins pushing microtubules apart and dynein pulling their minus ends together—create a tension that drives the self-organization of the initially disordered microtubule network into a classic bipolar, fusiform spindle apparatus (Walczak et al., 1998). This motor-driven sorting mechanism is so robust that it can form bipolar spindles around DNA-coated beads in *Xenopus* egg extracts, which lack centrioles, demonstrating the sufficiency of chromatin and motor proteins for this process (Heald et al., 1996).

Evolutionary Conservation and Robustness

The acentrosomal mechanism of spindle assembly employed by planarian neoblasts is not an evolutionary novelty but a deeply conserved pathway utilized across diverse eukaryotic lineages. It is the predominant mode of spindle formation in the female meiosis of most animal species, including humans, where oocytes arrest in metaphase II for extended periods without the aid of canonical centrosomes (Schuh & Ellenberg, 2007). The oocytes of the fruit fly *Drosophila melanogaster* represent a classic and well-studied model for acentrosomal spindle assembly, relying entirely on the RanGTP pathway and motor-driven self-organization (McKim & Hawley, 1995). Furthermore, higher plants, which naturally lack centrioles entirely, form bipolar spindles through mechanisms strikingly similar to those described for neoblasts, utilizing chromatin-mediated nucleation and microtubule reorganization into bipolar arrays (Petrovská et al., 2014).

This widespread phylogenetic conservation underscores the robustness and fidelity of the acentrosomal pathway. It is an ancient and reliable system that was likely the primordial method of cell division before the evolution of centrioles and centrosomes. The fact that planarian neoblasts, as well as the early embryonic cells of many mammals, utilize this pathway suggests that it may be particularly advantageous in certain stem cell contexts. Its reliability negates the notion that acentriolar division is inherently error-prone; on the contrary, in the specific cellular environment of the neoblast, it is a highly precise and controlled process. The reactivation of this ancient, conserved machinery in planarian stem cells may therefore be a key adaptation that permits their prolific and sustained proliferation throughout the animal's life, free from the constraints of centriole duplication and the risks of centrosome amplification.

Advantages of Acentriolar Division for Stem Cells

The acentriolar nature of planarian neoblasts, once considered a curious anomaly, may in fact represent a sophisticated evolutionary adaptation that confers specific advantages to the stem cell system. The absence of centrioles is not merely a passive loss but could be an active strategy that optimizes neoblast function for their critical roles in maintenance and regeneration. This chapter explores the potential selective benefits of acentrosomal division, including the enforcement of asymmetric cell fate outcomes, metabolic economy, and the suppression of oncogenic transformation.

Preventing Improper Division: Enforcing Asymmetry

A fundamental requirement for maintaining a stable pool of adult stem cells is the precise regulation of division symmetry. While symmetric divisions (which produce two identical stem cells or two differentiated cells) are necessary for expanding the population during growth or regeneration, asymmetric cell division (ACD) is crucial for self-renewal, where one stem cell gives rise to one stem cell and one differentiated progeny (Knoblich, 2010). In many canonical stem cell systems, the centrosome plays a direct role in ACD. The mother centriole, often retained in the stem cell daughter, is associated with specific fate determinants and its asymmetric segregation is a key mechanism for generating daughter cells with different identities (Yamashita et al., 2007).

The absence of centrioles in neoblasts may therefore be a mechanism to circumvent the default, centrosome-influenced pathways of division and impose a distinct, potentially more robust, mechanism for ensuring asymmetric outcomes. Without centrioles, the neoblast must rely on alternative polarity cues, such as cortical polarity complexes and the asymmetric segregation of mRNA and protein determinants, to dictate cell fate (Gönczy, 2008). It is plausible that the acentriolar state forces the cell to utilize these alternative pathways, which might be less prone to errors that could lead to expansion of the stem cell pool and potential tumorigenesis. In essence, by removing the centrosome—a potent organizer of division symmetry—from the equation, the planarian may have evolved a system where the decision to divide symmetrically or asymmetrically is more tightly coupled to extrinsic signals from the niche and intrinsic polarity networks that are less error-prone than centriole-based mechanisms (Morrison & Kimble, 2006). This could be particularly important in an organism like a planarian, where the stem cell population is vast and must be meticulously controlled.

Energetic Economy: Optimizing Resources for Proliferation

The biogenesis and maintenance of centrioles is a metabolically expensive process. It requires the coordinated synthesis of numerous proteins, their correct assembly into a complex structure, and the faithful duplication of that structure once per cell cycle (Nigg & Holland, 2018). This consumes energy (ATP), building blocks (amino acids), and transcriptional/translational capacity. For a cell like the neoblast, which must be poised to rapidly proliferate in response to

injury or during normal homeostasis, minimizing unnecessary energetic overhead could provide a significant selective advantage.

By eliminating centrioles, neoblasts free up cellular resources that can be reallocated to core functions essential for their stemness and proliferative capacity. These resources can be directed towards the massive transcriptional activity required to maintain pluripotency (as evidenced by their large, active nucleus), the rapid translation of proteins needed for cell cycle progression, and the synthesis of nucleotides for DNA replication (Shcherbik et al., 2016). This metabolic efficiency is not just a theoretical benefit; cancer cells, for instance, often rewire their metabolism to support their high proliferative demand (Vander Heiden et al., 2009). For neoblasts, operating under the constant constraint of resource allocation within the organism, the loss of centrioles could be a key part of a metabolic strategy that optimizes them for their function as a constant, on-demand source of new cells, allowing for a faster response to environmental cues like wounding.

Reducing Oncogenic Potential: Enhancing Fidelity and Control

Perhaps the most significant advantage of acentriolar division is the potential to reduce oncogenic risk. In most animal cells, centrosome amplification—the acquisition of more than two centrosomes—is a common feature of cancers and a potent driver of chromosomal instability (CIN). Supernumerary centrosomes can lead to multipolar spindles, merotelic kinetochore attachments, and aneuploidy, all of which fuel tumor evolution (Godinho & Pellman, 2014). The very process of centriole duplication is a node of vulnerability; dysregulation of key regulators like PLK4 can easily lead to centriole overduplication (Basto et al., 2008).

Neoblasts are effectively immune to this entire class of oncogenic defects. They cannot undergo centrosome amplification because they lack the template and the core machinery to make centrioles in the first place. Their acentrosomal spindle assembly pathway, reliant on chromatin and motor-driven self-organization, may be inherently more robust and less susceptible to the formation of unstable multipolar configurations. The spindle bipolarity is an emergent property of the system rather than being dictated by the number of pre-existing organelles (Müller-Reichert et al., 2022). This could provide a crucial safeguard for a long-lived organism like a planarian, whose somatic cells are post-mitotic and whose entire regenerative capacity depends on the genomic integrity of its neoblasts over its potentially indefinite lifespan. The absence of centrioles may thus be a tumor-suppressor mechanism, a way to eliminate a major source of genomic instability from the proliferative compartment of the animal (Levine & Holland, 2018). The fact that planarians appear to be highly resistant to spontaneous tumor formation, despite their massive and lifelong proliferative potential, lends credence to the idea that their unique stem cell biology, including acentriolar division, is inherently protective (Pearson & Sánchez Alvarado, 2010).

In conclusion, the lack of centrioles in neoblasts is unlikely to be a mere evolutionary relic. Instead, it appears to be an adaptive trait that positively contributes to their function by promoting asymmetric division, conserving energy, and most importantly, providing a powerful barrier

against genomic instability and cancer. This unique adaptation highlights how fundamental cellular processes can be remodeled in specific contexts to optimize fitness and ensure long-term tissue homeostasis.

Why Differentiated Cells with Centrioles Do Not Divide

The inverse correlation in planarians—where proliferative cells lack centrioles and centriole-bearing cells are post-mitotic—demands an explanation for the quiescence of the differentiated compartment. The presence of a centriole, the organelle canonically required for division, in these non-dividing cells is a profound paradox. The evidence strongly suggests that the centriole is not the cause of this cell cycle exit but rather a consequence of it. The terminal differentiation program itself imposes a deep and multifaceted block on proliferation, rendering the centrioles functionally redundant for mitosis and repurposing them for alternative cellular functions.

Epigenetic Reprogramming and Cell Cycle Silencing

The journey from a pluripotent neoblast to a terminally differentiated cell involves a radical rewiring of the gene expression landscape, governed largely by epigenetic mechanisms. This reprogramming permanently silences the vast machinery required for cell cycle progression and DNA replication. Differentiated cells downregulate the core regulators of the cell cycle, including cyclins and cyclin-dependent kinases (CDKs), which are essential for driving the cell through its phases (G1, S, G2, M) (Malumbres & Barbacid, 2009). For instance, the expression of mitotic cyclins (e.g., Cyclin B) and S-phase promoting factors is extinguished.

This silencing is enforced through stable epigenetic marks. Histone modifications, such as the repressive trimethylation of histone H3 on lysine 27 (H3K27me3), are deposited on the promoters of cell cycle and proliferation-related genes, locking them in a transcriptionally inactive state (Onal et al., 2012). Additionally, the retinoblastoma (Rb) tumor suppressor pathway, a key guardian of the G1/S checkpoint, is likely activated and maintained in a hypophosphorylated state in differentiated cells. Active Rb binds and inhibits transcription factors like E2F, which are necessary for the expression of S-phase genes (e.g., DNA polymerase, replication origin factors), thus effectively blocking any attempt to initiate DNA replication (Burkhart & Sage, 2008). This epigenetic and regulatory lockdown ensures that the molecular engine of the cell cycle is completely disassembled, making re-entry into the cycle virtually impossible.

Centrioles as a Marker of Differentiation, Not a Cause of Quiescence

The acquisition of centrioles in differentiated planarian cells is best understood not as the reason they cannot divide, but as a hallmark of their terminal state. These cells synthesize centrioles *de novo* to serve specialized, post-mitotic functions, most notably as basal bodies for ciliogenesis. The planarian epidermis, for example, is a densely ciliated epithelium that facilitates locomotion through the coordinated beating of cilia, all nucleated by centriole-derived basal bodies (Rink et al., 2009; Gonzalez-Sastre et al., 2017). Similarly, cells of the protonephridial system (the planarian kidney) use cilia for generating fluid flow.

The molecular pathways that drive terminal differentiation also activate the program for centriole biogenesis and cilia formation. The transcription factor FoxJ1, a master regulator of motile ciliogenesis, is expressed in these differentiated ciliated cells and upregulates genes necessary for centriole duplication and ciliary assembly (Vladar & Brody, 2013). Therefore, the centriole is a product of the differentiation process itself. It is a piece of specialized cellular equipment acquired for a specific job, much like a neuron acquires synaptic vesicles or a muscle cell acquires myofibrils. Its presence is a signature that the cell has committed to a complex, functional role within the organism's soma, a role that is incompatible with the disruptive process of mitosis.

Irreversible Exit from the Cell Cycle and Centriole Repurposing

Differentiated planarian cells enter a state of deep and likely irreversible quiescence (G0). Their centrioles are never recruited to function as MTOCs for spindle assembly because the entire mitotic program is epigenetically disabled. The centrioles are molecularly "asleep" in their capacity to nucleate microtubules for mitosis. Instead, they are fully dedicated to their role in anchoring and organizing the axonemal microtubules of the cilium.

This post-mitotic state is fiercely protected by robust tumor suppressor mechanisms. The planarian homolog of the p53 protein, a key guardian of genomic integrity and a potent cell cycle inhibitor, is expressed in differentiated tissues and is thought to play a crucial role in maintaining this quiescence (Pearson & Sánchez Alvarado, 2010). p53 can arrest the cell cycle in response to stress and DNA damage, and its sustained activity in differentiated cells provides a powerful barrier against any aberrant attempt to re-enter the cell cycle, which would be catastrophic for tissue function.

Attempts to experimentally force these cells to divide would likely fail or induce apoptosis. Even if one could theoretically reactivate the cell cycle machinery, the centrioles in these cells have been repurposed and may not be immediately competent to form a mitotic centrosome. They are stably anchored at the cell membrane as basal bodies, and their associated pericentriolar material (PCM) is configured for ciliogenesis, not for the massive microtubule nucleation required for mitosis (Vertii et al., 2016). Dismantling this ciliary apparatus to convert a basal

body back into a centrosome is a complex process that is not part of the planarian differentiated cell's program.

In conclusion, the centrioles in differentiated planarian cells are passengers, not drivers, of the post-mitotic state. Their presence is a consequence of a terminal differentiation program that epigenetically silences the cell cycle and simultaneously activates pathways for building specialized structures like cilia. The irreversible exit from the cell cycle is enforced by powerful tumor suppressor networks like p53. Thus, the planarian body is elegantly organized into two discrete compartments: one dedicated to proliferation (acentriolar neoblasts) and one dedicated to function (centriolar somatic cells), with the differentiation process acting as a strict one-way valve between them.

Comparison with Other Biological Systems

The planarian strategy of acentriolar stem cell division is not an isolated biological curiosity. Rather, it represents a specific implementation of a broader, evolutionarily conserved phenomenon. Placing the planarian neoblast system in a comparative context with other biological models—ranging from early mammalian development to cancer pathology and other stem cell types—reveals fundamental principles about the regulation of cell division, the functionality of acentrosomal pathways, and the potential advantages of sidestepping centriole dependency in certain contexts.

Early Mammalian Embryogenesis: A Transient Phase of Acentrosomal Division

The most striking parallel to planarian neoblast division is found in the very beginning of mammalian life. The early cleavages of the zygote and blastomeres in mice, humans, and other mammals occur in the absence of canonical centrioles (Courtois et al., 2012). The sperm contributes a centriole, but it is degraded after fertilization. The oocyte is naturally acentriolar, and as a result, the first several cell divisions rely entirely on acentrosomal mechanisms to form bipolar spindles (Schuh & Ellenberg, 2007). These early embryonic spindles are assembled through mechanisms highly reminiscent of those in planarian neoblasts: microtubules are nucleated around chromosomes via the RanGTP pathway and are then organized into bipolar arrays by the action of motor proteins like kinesin-5 and dynein (Holubcová et al., 2015).

Centrioles only appear *de novo* later in development, around the time of blastocyst formation, coinciding with a major transcriptional activation event known as the maternal-to-zygotic transition (MZT) and the onset of cellular differentiation (Loncarek & Khodjakov, 2009). This developmental timeline is profoundly instructive. It demonstrates that acentrosomal spindle assembly is a robust and precise enough mechanism to support the critical initial divisions that form an organism. Furthermore, it establishes a clear correlation: the pluripotent, rapidly dividing cells of the early embryo are acentriolar, while the appearance of centrioles is coupled with the

onset of differentiation. This echoes the planarian paradigm exactly, suggesting that the absence of centrioles may be a conserved feature of certain potent, plastic proliferative states.

Cancer Cells: Centrosome Amplification as a Source of Instability

A revealing counterpoint to the stable acentriolar division of neoblasts is the situation in many cancer cells. A hallmark of numerous carcinomas, sarcomas, and hematological malignancies is centrosome amplification—the presence of more than two centrosomes (Godinho & Pellman, 2014). This aberration occurs due to defects in the strict regulatory cycle that controls centriole duplication, often driven by oncogene activation or tumor suppressor inactivation (Nigg & Holland, 2018).

Supernumerary centrosomes are a potent driver of chromosomal instability (CIN). They can organize multipolar spindles that lead to catastrophic mitotic errors, or they can cluster into pseudo-bipolar spindles that nevertheless foster merotelic kinetochore attachments (where a single kinetochore is attached to microtubules from both poles) (Ganem et al., 2009). These erroneous attachments lag behind in anaphase, leading to DNA breakage and whole-chromosome mis-segregation, thus fueling tumor heterogeneity and evolution (Levine & Holland, 2018).

The contrast with planarian neoblasts is stark. Neoblasts have evolutionarily jettisoned the entire centriole duplication machinery, eliminating the very possibility of centrosome amplification. Their acentrosomal pathway, reliant on chromatin and self-organization, is inherently constrained to form a bipolar array. This suggests that one of the significant advantages of acentriolar division is the avoidance of a major source of genomic instability. The neoblast system demonstrates that prolific proliferation can be decoupled from the risk of centrosome-driven CIN, a decoupling that cancer cells, with their dysregulated centriole cycles, disastrously fail to achieve.

Drosophila Male Germline Stem Cells: A Shared Stem Cell Strategy

Further evidence that acentriolar division may be a specialized feature of certain stem cell niches comes from the model organism *Drosophila melanogaster*. The male germline stem cells (GSCs) in the *Drosophila* testis, which are responsible for sustained spermatogenesis, also divide without centrioles (Yamashita et al., 2007). In this system, the mother centriole is asymmetrically inherited by the differentiating gonblast cell during each stem cell division. The stem cell daughter is left without a centriole and must therefore undergo acentrosomal mitosis to proliferate.

This mechanism ensures that the stem cell property is associated with the acentriolar state, while the acquisition of a centriole is a marker of commitment to differentiation—a principle that directly mirrors the planarian system. The *Drosophila* male GSC niche provides a clear example where the asymmetric segregation of a centriole is used to enforce asymmetric cell fate, and the

stem cell relies on acentrosomal mechanisms for its self-renewing divisions (Venkei & Yamashita, 2018). This convergent evolution between a fly and a flatworm strongly implies that acentriolar division is not a random loss but a adaptive trait that may be particularly advantageous in maintaining specific types of stem cell populations. It may facilitate the precise asymmetric segregation of fate determinants or, as in planarians, reduce the metabolic cost and oncogenic risk associated with maintaining the centriole duplication cycle.

In summary, the planarian neoblast system is a key piece in a broader puzzle of acentrosomal life. It shares a developmental strategy with the earliest stages of mammalian life, represents a stable alternative to the centrosome-driven chaos of cancer, and exhibits a convergent evolutionary solution with the stem cells of the *Drosophila* male germline. These comparisons affirm that acentriolar division is a widespread, robust, and controlled biological phenomenon, and its employment in planarian neoblasts is a key adaptation for their lifelong regenerative capacity.

Consequences and Biological Significance

The unique cellular dichotomy observed in planarians—acentriolar, proliferative neoblasts versus centriolar, post-mitotic somatic cells—is not merely a biological oddity. It represents a profound evolutionary adaptation with significant implications for our understanding of stem cell biology, regeneration, and the fundamental principles of cell cycle control. The biological significance of this system extends from the organismal level, explaining the remarkable regenerative capacity of planarians, to the conceptual level, offering new paradigms for biomedical research.

Regenerative Potential and Long-Term Genomic Stability

The ability to undergo acentriolar division is likely a fundamental property that underpins the long-term maintenance of a potent stem cell pool in planarians. The neoblast population must persist and function flawlessly throughout the animal's life, which is essentially indefinite under ideal conditions (Reddien, 2018). This presents a formidable challenge: how to sustain massive proliferative potential over a lifetime without succumbing to the genomic instability that typically accompanies high rates of cell division.

The avoidance of centrioles provides a elegant solution to this challenge. As discussed, the acentrosomal pathway of spindle assembly is inherently resistant to the formation of multipolar spindles, a major source of chromosomal instability (CIN) and a hallmark of many cancers (Godinho & Pellman, 2014). By eliminating the centriole duplication cycle, neoblasts effectively bypass the risk of centrosome amplification, a potent driver of aneuploidy (Levine & Holland, 2018). This may be a key reason why planarians, despite their immense regenerative activity, exhibit extreme resistance to spontaneous tumor formation (Pearson & Sánchez Alvarado, 2010). The neoblast system demonstrates that high proliferative capacity and genomic stability are not mutually exclusive; they can be synergistically achieved through the evolutionary loss of

a potentially error-prone organelle. This strategy allows for the maintenance of a large, perpetually active stem cell population that is both highly potent and remarkably secure, forming the cellular basis for their legendary regenerative capabilities.

Evolutionary Plasticity and the Diversification of Regenerative Strategies

The adoption of acentrosomal division likely provided a significant evolutionary advantage, enabling the diversification and refinement of regenerative mechanisms in planarians and similar organisms. The centriole is a complex organelle whose duplication, maturation, and function are governed by a tightly regulated and costly genetic program (Nigg & Holland, 2018). Freeing stem cells from these constraints may have provided greater evolutionary plasticity.

Without the need to coordinate spindle assembly with the centriole cycle, neoblasts could potentially respond more rapidly to regenerative cues. The signaling pathways activating proliferation could directly engage the core cell cycle and acentrosomal spindle assembly machinery without an intermediary organellar duplication step, potentially speeding up the initial response to injury (Wenemoser & Reddien, 2010). Furthermore, the molecular resources saved by not synthesizing centriolar components could be reallocated to other functions, such as the expression of a vast repertoire of genes that maintain pluripotency and enable differentiation into any cell type (Labbe et al., 2012). This evolutionary flexibility might have been a prerequisite for the development of such a powerful and comprehensive regenerative system, allowing stem cell biology to be optimized for function over strict adherence to a canonical mitotic mechanism.

Directions for Medicine: Insights for Regenerative Medicine and Oncology

The lessons from planarian neoblasts offer fertile ground for translational research in two seemingly opposed fields: regenerative medicine and oncology. Understanding the mechanisms of acentriolar division could provide new strategies for controlling stem cell behavior in therapeutic contexts.

In regenerative medicine, a primary goal is to control the proliferation and differentiation of stem cells for tissue repair. The planarian model suggests that promoting a transient, acentrosomal state in human stem or progenitor cells might be a way to expand these populations in vitro or in vivo while minimizing the risk of genomic instability and transformation (Iismaa et al., 2018). Identifying the key regulators that allow neoblasts to divide faithfully without centrioles could reveal novel targets for enhancing the safety and efficacy of stem cell-based therapies.

Conversely, in oncology, the goal is often to inhibit proliferation. Many aggressive cancers rely on centrosome amplification for their survival and evolution (Godinho & Pellman, 2014). The planarian system highlights the viability of a proliferation pathway that does not depend on

centrioles. This raises a provocative question: could forcing cancer cells with extra centrosomes to revert to an acentrosomal mode of division be a therapeutic strategy? Such a switch could potentially mitigate the chromosomal instability that drives tumor aggression and drug resistance. Alternatively, the vulnerabilities of cancer cells with supernumerary centrosomes could be exploited; these cells are dependent on specific mechanisms, such as centrosome clustering, to survive mitosis. Targeted therapies against proteins like HSET (a kinesin involved in clustering) are already being explored to specifically kill cancer cells with amplified centrosomes by inducing lethal multipolar divisions (Kwon et al., 2008). The planarian paradox, by throwing the problems of centrosome amplification into sharp relief, helps validate this entire approach to targeted cancer therapy.

In conclusion, the biological significance of the planarian system extends far beyond the organism itself. It provides a powerful example of how evolution can rewire fundamental cellular processes to achieve remarkable organismal feats like whole-body regeneration. It challenges the dogma that centrioles are indispensable for mitosis and instead presents acentrosomal division as a stable, advantageous strategy for specific cellular contexts. Finally, it offers a fresh perspective and novel conceptual frameworks for addressing some of the most pressing challenges in human medicine, from regenerating damaged tissues to eliminating cancerous growths.

Conclusion and Future Perspectives

The investigation into the planarian cellular paradox reveals a sophisticated biological system where the conventional rules of cell division are elegantly subverted to meet the unique demands of whole-body regeneration and lifelong homeostasis. The findings synthesized in this review demonstrate that the acentriolar nature of neoblasts is not a developmental deficiency but a refined evolutionary adaptation, while the quiescence of centriole-bearing somatic cells is a consequence of terminal differentiation, not organelle possession.

Summary of Findings

The central conclusion of this analysis is that the planarian system represents a profound uncoupling of the mitotic apparatus from the centriole. Neoblasts, the drivers of planarian immortality, have evolutionarily lost their centrioles and instead utilize a robust, acentrosomal pathway for spindle assembly (Azimzadeh et al., 2012). This mechanism, reliant on chromatin-mediated nucleation via the RanGTP pathway and motor protein-driven self-organization, is both highly efficient and accurate (Müller-Reichert et al., 2022). This adaptation likely confers significant advantages, including a reduced risk of centrosome amplification-driven genomic instability, metabolic economy, and potentially a more facile execution of asymmetric cell divisions (Godinho & Pellman, 2014; Nigg & Holland, 2018).

Conversely, the post-mitotic state of differentiated cells is not caused by their centrioles but is a hallmark of their terminal identity. These cells acquire centrioles *de novo* to serve as basal

bodies for cilia, essential structures for planarian locomotion and osmoregulation (Rink et al., 2009). Their exit from the cell cycle is enforced by deep epigenetic reprogramming that silences core cell cycle genes and is maintained by powerful tumor suppressor networks like the p53 pathway (Onal et al., 2012; Pearson & Sánchez Alvarado, 2010). The presence of centrioles is thus a correlate, not a cause, of their differentiated status.

Unresolved Questions and Future Research Directions

Despite significant advances, the planarian system presents numerous compelling questions that warrant further investigation.

First, what is the complete genetic repertoire controlling the acentrosomal switch in neoblasts? While the broad mechanisms (RanGTP, motor proteins) are known from other models, the specific genes that enable neoblasts to permanently forgo centriole biogenesis and perfect this mode of division remain largely unidentified. Are there specific "acentriolar" factors yet to be discovered? High-resolution single-cell RNA sequencing (scRNA-seq) of neoblasts at different cell cycle stages could provide a complete transcriptomic profile, revealing uniquely expressed genes that are essential for acentrosomal spindle assembly (Plass et al., 2018). Subsequent functional RNA interference (RNAi) screens targeting these candidates could identify key regulators whose loss disrupts mitotic fidelity in neoblasts but not in canonical cells.

Second, how is the high fidelity of chromosome segregation achieved without centrioles? The precision of the process must be extraordinary to prevent the accumulation of mutations over the planarian's indefinite lifespan. Advanced live-cell imaging using transgenic planarians expressing fluorescent tags for tubulin, kinetochores, and chromosomes will be crucial for visualizing spindle dynamics and chromosome movements in real-time in vivo (Müller-Reichert et al., 2022). This could reveal potential compensatory mechanisms or novel checkpoint controls that ensure accuracy in the absence of centrosomes.

Third, are there signals from the differentiated tissue environment that actively reinforce the post-mitotic state? While intrinsic epigenetic blocks are key, it is plausible that the surrounding somatic tissue secretes factors that help maintain quiescence. Investigating the crosstalk between neoblasts and their niche, and between differentiated cells themselves, could reveal paracrine signals that suppress any latent potential for proliferation in centriole-bearing cells, providing an additional layer of security against aberrant division.

Finally, a broader question persists: is the loss of centrioles a prerequisite for the evolution of such extreme regenerative capacity? Comparative studies with other highly regenerative organisms (e.g., acoels, hydra, and certain vertebrates like axolotls) could determine if acentriolar division in adult stem cells is a convergent evolutionary strategy or a unique invention of the planarian lineage.

Concluding Remarks

The planarian, a humble flatworm, continues to offer profound insights into fundamental cell biology. Its violation of the long-held rule that animal cell division requires centrioles has forced a reevaluation of mitotic mechanisms and highlighted the remarkable plasticity of eukaryotic cells. The neoblast system demonstrates that proliferation and genomic stability can be enhanced by the evolutionary loss of a complex organelle. It provides a powerful natural example of how a stem cell population can be optimized for function, safety, and longevity. The continued study of this paradox will not only illuminate the intricacies of planarian biology but will also provide fundamental insights with the potential to inform new strategies in regenerative medicine and cancer therapy, proving that some of the most advanced biological solutions can be found in the most ancient of creatures.

References:

- Ahmad, F. J., & Baas, P. W. (1995). Microtubules released from the neuronal centrosome are transported into the axon. *Journal of Cell Science*, *108*(Pt 8), 2761–2769. <https://doi.org/10.1242/jcs.108.8.2761>
- Aphkhazava, D., Sulashvili, N., & Tkemaladze, J. (2025). Stem Cell Systems and Regeneration. *Georgian Scientists*, 7(1), 271–319. doi: <https://doi.org/10.52340/gs.2025.07.01.26>
- Aphkhazava, D., Sulashvili, N., Maglakelidze, G., & Tkemaladze, J. (2025). Ageless Creatures: Molecular Insights into Organisms That Defy Aging. *Georgian Scientists*, 7(3), 346–396. doi: <https://doi.org/10.52340/gs.2025.07.03.24>
- Azimzadeh, J., Wong, M. L., Downhour, D. M., Sánchez Alvarado, A., & Marshall, W. F. (2012). Centrosome loss in the evolution of planarians. *Science*, *335*(6067), 461–463. <https://doi.org/10.1126/science.1214457>
- Basto, R., Brunk, K., Vinadogrova, T., Peel, N., Franz, A., Khodjakov, A., & Raff, J. W. (2008). Centrosome amplification can initiate tumorigenesis in flies. *Cell*, *133*(6), 1032–1042. <https://doi.org/10.1016/j.cell.2008.05.039>
- Burbank, K. S., Mitchison, T. J., & Fisher, D. S. (2007). Slide-and-cluster models for spindle assembly. *Current Biology*, *17*(16), 1373–1383. <https://doi.org/10.1016/j.cub.2007.07.058>
- Burkhardt, D. L., & Sage, J. (2008). Cellular mechanisms of tumour suppression by the retinoblastoma gene. *Nature Reviews Cancer*, *8*(9), 671–682. <https://doi.org/10.1038/nrc2399>
- Caudron, M., Bunt, G., Bastiaens, P., & Karsenti, E. (2005). Spatial coordination of spindle assembly by chromosome-mediated signaling gradients. *Science*, *309*(5739), 1373–1376. <https://doi.org/10.1126/science.1115964>
- Chichinadze, K., Lazarashvili, A., & Tkemaladze, J. (2013). RNA in centrosomes: structure and possible functions. *Protoplasma*, 250(1), 397–405.
- Chichinadze, K., Tkemaladze, D., & Lazarashvili, A. (2012). New class of RNA and centrosomal hypothesis of cell aging. *Advances in Gerontology= Uspekhi Gerontologii*, 25(1), 23–28.
- Chichinadze, K., Tkemaladze, J., & Lazarashvili, A. (2012). A new class of RNAs and the centrosomal hypothesis of cell aging. *Advances in Gerontology*, 2(4), 287–291.
- Chichinadze, K., Tkemaladze, J., & Lazarashvili, A. (2012). Discovery of centrosomal RNA and centrosomal hypothesis of cellular ageing and differentiation. *Nucleosides, Nucleotides and Nucleic Acids*, 31(3), 172–183.
- Chichinadze, K. N., & Tkemaladze, D. V. (2008). Centrosomal hypothesis of cellular aging and differentiation. *Advances in Gerontology= Uspekhi Gerontologii*, 21(3), 367–371.
- Clarke, P. R., & Zhang, C. (2008). Spatial and temporal coordination of mitosis by Ran GTPase. *Nature Reviews Molecular Cell Biology*, *9*(6), 464–477. <https://doi.org/10.1038/nrm2410>
- Conduit, P. T., Wainman, A., & Raff, J. W. (2015). Centrosome function and assembly in animal cells. *Nature Reviews Molecular Cell Biology*, *16*(10), 611–624. <https://doi.org/10.1038/nrm4062>
- Courtois, A., Schuh, M., Ellenberg, J., & Hiiragi, T. (2012). The transition from meiotic to mitotic spindle assembly is gradual during early mammalian development. *The Journal of Cell Biology*, *198*(3), 357–370. <https://doi.org/10.1083/jcb.201202135>

Cowles, M. W., Brown, D. D., Nisperos, S. V., Stanley, B. N., Pearson, B. J., & Zayas, R. M. (2013). Genome-wide analysis of the bHLH gene family in planarians identifies factors required for adult neurogenesis and neuronal regeneration. *Development*, *140*(23), 4691–4702. <https://doi.org/10.1242/dev.098616>

Dumont, J., & Desai, A. (2012). Acentrosomal spindle assembly and chromosome segregation during oocyte meiosis. *Trends in Cell Biology*, *22*(5), 241–249. <https://doi.org/10.1016/j.tcb.2012.02.007>

Elfettahi, A. . E., & Tkemaladze, J. (2025). The Neuro-Hepatic-Affective Model (NHAM): A Systems Framework for Liver–Brain Modulation of Emotion in Precision Psychiatry. Preprints. doi: <https://doi.org/10.20944/preprints202508.1312.v1>

Elliott, S. A., & Sánchez Alvarado, A. (2013). The history and enduring contributions of planarians to the study of animal regeneration. *Wiley Interdisciplinary Reviews: Developmental Biology*, *2*(3), 301–326. <https://doi.org/10.1002/wdev.82>

Gaglio, T., Saredi, A., & Compton, D. A. (1996). NuMA is required for the organization of microtubules into aster-like mitotic arrays. *The Journal of Cell Biology*, *131*(3), 693–708. <https://doi.org/10.1083/jcb.131.3.693>

Ganem, N. J., Godinho, S. A., & Pellman, D. (2009). A mechanism linking extra centrosomes to chromosomal instability. *Nature*, *460*(7252), 278–282. <https://doi.org/10.1038/nature08136>

Gentile, L., Cebrià, F., & Bartscherer, K. (2011). The planarian flatworm: an in vivo model for stem cell biology and nervous system regeneration. *Disease Models & Mechanisms*, *4*(1), 12–19. <https://doi.org/10.1242/dmm.006692>

Godinho, S. A., & Pellman, D. (2014). Causes and consequences of centrosome abnormalities in cancer. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *369*(1650), 20130467. <https://doi.org/10.1098/rstb.2013.0467>

Gonzalez-Sastre, A., de Sousa, N., Adell, T., & Saló, E. (2017). The mystery of the regeneration of the planarian excretory system. *Developmental Biology*, *433*(2), 394–403. <https://doi.org/10.1016/j.ydbio.2017.07.023>

Grill, S. W., Gönczy, P., Stelzer, E. H., & Hyman, A. A. (2001). Polarity controls forces governing asymmetric spindle positioning in the *Caenorhabditis elegans* embryo. *Nature*, *409*(6820), 630–633. <https://doi.org/10.1038/35054572>

Gönczy, P. (2008). Mechanisms of asymmetric cell division: flies and worms pave the way. *Nature Reviews Molecular Cell Biology*, *9*(11), 855–868. <https://doi.org/10.1038/nrm2524>

Heald, R., Tournéize, R., Blank, T., Sandaltzopoulos, R., Becker, P., Hyman, A., & Karsenti, E. (1996). Self-organization of microtubules into bipolar spindles around artificial chromosomes in *Xenopus* egg extracts. *Nature*, *382*(6590), 420–425. <https://doi.org/10.1038/382420a0>

Holubcová, Z., Blayney, M., Elder, K., & Schuh, M. (2015). Human oocytes. Error-prone chromosome-mediated spindle assembly favors chromosome segregation defects in human oocytes. *Science*, *348*(6239), 1143–1147. <https://doi.org/10.1126/science.aaa9529>

Iismaa, S. E., Kaidonis, X., Nicks, A. M., Bogush, N., Kikuchi, K., Naqvi, N., Harvey, R. P., Husain, A., & Graham, R. M. (2018). Comparative regenerative mechanisms across different mammalian tissues. *NPJ Regenerative Medicine*, *3*, 6. <https://doi.org/10.1038/s41536-018-0044-5>

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.

Juliano, C. E., Swartz, S. Z., & Wessel, G. M. (2011). A conserved germline multipotency program. *Development*, *138*(24), 5423–5433. <https://doi.org/10.1242/dev.068049>

Kipshidze, M., & Tkemaladze, J. (2023). Comparative Analysis of drugs that improve the Quality of Life and Life Expectancy. *Junior Researchers*, 1(1), 184–193. doi: <https://doi.org/10.52340/2023.01.01.19>

Kipshidze, M., & Tkemaladze, J. (2023). The planaria *Schmidtea mediterranea* as a model system for the study of stem cell biology. *Junior Researchers*, 1(1), 194–218. doi: <https://doi.org/10.52340/2023.01.01.20>

Kipshidze, M., & Tkemaladze, J. (2024). Abastumani Resort: Balneological Heritage and Modern Potential. *Junior Researchers*, 2(2), 126–134. doi: <https://doi.org/10.52340/jr.2024.02.02.12>

Kipshidze, M., & Tkemaladze, J. (2024). Balneology in Georgia: traditions and modern situation. *Junior Researchers*, 2(2), 78–97. doi: <https://doi.org/10.52340/jr.2024.02.02.09>

Kipshidze, M., & Tkemaladze, J. (2024). Microelementoses - history and current status. *Junior Researchers*, 2(2), 108–125. doi: <https://doi.org/10.52340/jr.2024.02.02.11>

Knoblich, J. A. (2010). Asymmetric cell division: recent developments and their implications for tumour biology. *Nature Reviews Molecular Cell Biology*, *11*(12), 849–860. <https://doi.org/10.1038/nrm3010>

Kwon, M., Godinho, S. A., Chandhok, N. S., Ganem, N. J., Azioune, A., Thery, M., & Pellman, D. (2008). Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes. *Genes & Development*, *22*(16), 2189–2203. <https://doi.org/10.1101/gad.1700908>

Labbe, R. M., Irimia, M., Currie, K. W., Lin, A., Zhu, S. J., Brown, D. D., Ross, E. J., Voisin, V., Bader, G. D., Blencowe, B. J., & Pearson, B. J. (2012). A comparative transcriptomic analysis reveals conserved features of stem cell pluripotency in planarians and mammals. *Stem Cells*, *30*(8), 1734-1745. <https://doi.org/10.1002/stem.1144>

Levine, M. S., & Holland, A. J. (2018). The impact of mitotic errors on cell proliferation and tumorigenesis. *Genes & Development*, *32*(9-10), 620-638. <https://doi.org/10.1101/gad.314351.118>

Lezhava, T., Monaselidze, J., Jokhadze, T., Kakauridze, N., Khodeli, N., Rogava, M., Tkemaladze, J., ... & Gaiozishvili, M. (2011). Gerontology research in Georgia. *Biogerontology*, 12, 87-91. doi: 10.1007/s10522-010-9283-6. Epub 2010 May 18. PMID: 20480236; PMCID: PMC3063552

Loncarek, J., & Khodjakov, A. (2009). Ab ovo or de novo? Mechanisms of centriole duplication. *Molecular Cells*, *27*(2), 135-142. <https://doi.org/10.1007/s10059-009-0017-z>

Malumbres, M., & Barbacid, M. (2009). Cell cycle, CDKs and cancer: a changing paradigm. *Nature Reviews Cancer*, *9*(3), 153-166. <https://doi.org/10.1038/nrc2602>

Matsaberidze, M., Prangishvili, A., Gasitashvili, Z., Chichinadze, K., & Tkemaladze, J. (2017). TO TOPOLOGY OF ANTI-TERRORIST AND ANTI-CRIMINAL TECHNOLOGY FOR EDUCATIONAL PROGRAMS. *International Journal of Terrorism & Political Hot Spots*, 12.

McKim, K. S., & Hawley, R. S. (1995). Chromosomal control of meiotic cell division. *Science*, *270*(5242), 1595-1601. <https://doi.org/10.1126/science.270.5242.1595>

Merdes, A., Ramyar, K., Vechio, J. D., & Cleveland, D. W. (1996). A complex of NuMA and cytoplasmic dynein is essential for mitotic spindle assembly. *Cell*, *87*(3), 447-458. [https://doi.org/10.1016/s0092-8674\(00\)81365-3](https://doi.org/10.1016/s0092-8674(00)81365-3)

Meunier, S., & Vernos, I. (2012). Microtubule assembly during mitosis - from distinct origins to distinct functions? *Journal of Cell Science*, *125*(Pt 12), 2805-2814. <https://doi.org/10.1242/jcs.092429>

Morrison, S. J., & Kimble, J. (2006). Asymmetric and symmetric stem-cell divisions in development and cancer. *Nature*, *441*(7097), 1068-1074. <https://doi.org/10.1038/nature04956>

Mountain, V., Simerly, C., Howard, L., Ando, A., Schatten, G., & Compton, D. A. (1999). The kinesin-related protein, HSET, opposes the activity of Eg5 and cross-links microtubules in the mammalian mitotic spindle. *The Journal of Cell Biology*, *147*(2), 351-366. <https://doi.org/10.1083/jcb.147.2.351>

Musacchio, A., & Desai, A. (2017). A molecular view of kinetochore assembly and function. *Biology*, *6*(1), 5. <https://doi.org/10.3390/biology6010005>

Müller-Reichert, T., Rütthmann, M., Matos, I., & Ozlü, N. (2022). The ultrastructure of the mitotic spindle and its implications for chromosome segregation in planarian stem cells. *Cells*, *11*(10), 1603. <https://doi.org/10.3390/cells11101603>

Newmark, P. A., & Sánchez Alvarado, A. (2002). Not your father's planarian: a classic model enters the era of functional genomics. *Nature Reviews Genetics*, *3*(3), 210-219. <https://doi.org/10.1038/nrg759>

Nigg, E. A., & Holland, A. J. (2018). Once and only once: mechanisms of centriole duplication and their deregulation in disease. *Nature Reviews Molecular Cell Biology*, *19*(5), 297-312. <https://doi.org/10.1038/nrm.2017.127>

Nigg, E. A., & Raff, J. W. (2009). Centrioles, centrosomes, and cilia in health and disease. *Cell*, *139*(4), 663-678. <https://doi.org/10.1016/j.cell.2009.10.036>

Onal, P., Grün, D., Adamidi, C., Rybak, A., Solana, J., Mastrobuoni, G., Wang, Y., Rahn, H. P., Chen, W., Kempa, S., Ziebold, U., & Rajewsky, N. (2012). Gene expression of pluripotency determinants is conserved between mammalian and planarian stem cells. *The EMBO Journal*, *31*(12), 2755-2769. <https://doi.org/10.1038/emboj.2012.110>

Pearson, B. J., & Sánchez Alvarado, A. (2010). A planarian p53 homolog regulates proliferation and self-renewal in adult stem cell lineages. *Development*, *137*(2), 213-221. <https://doi.org/10.1242/dev.044297>

Petrovská, B., Černá, H., & Seifertová, D. (2014). From microtubule to the cell shape: the role of plant-specific microtubule-associated proteins in shaping plant cells. *New Phytologist*, *203*(1), 66-80. <https://doi.org/10.1111/nph.12789>

Plass, M., Solana, J., Wolf, F. A., Ayoub, S., Misios, A., Glažar, P., Obermayer, B., Theis, F. J., Kocks, C., & Rajewsky, N. (2018). Cell type atlas and lineage tree of a whole complex animal by single-cell transcriptomics. *Science*, *360*(6391), eaq1723. <https://doi.org/10.1126/science.aq1723>

Prangishvili, A., Gasitashvili, Z., Matsaberidze, M., Chkhartishvili, L., Chichinadze, K., Tkemaladze, J., ... & Azmaiparashvili, Z. (2019). SYSTEM COMPONENTS OF HEALTH AND INNOVATION FOR THE ORGANIZATION OF NANO-BIOMEDIC ECOSYSTEM TECHNOLOGICAL PLATFORM. *Current Politics and Economics of Russia, Eastern and Central Europe*, 34(2/3), 299-305.

Prosser, S. L., & Pelletier, L. (2017). Mitotic spindle assembly in animal cells: a fine balancing act. *Nature Reviews Molecular Cell Biology*, *18*(3), 187-201. <https://doi.org/10.1038/nrm.2016.162>

Reddien, P. W. (2018). The cellular and molecular basis for planarian regeneration. *Cell*, *175*(2), 327-345. <https://doi.org/10.1016/j.cell.2018.09.021>

Reddien, P. W., Bermange, A. L., Murfitt, K. J., Jennings, J. R., & Sánchez Alvarado, A. (2005). Identification of genes needed for regeneration, stem cell function, and tissue homeostasis by systematic gene perturbation in planaria. *Developmental Cell*, *8*(5), 635-649. <https://doi.org/10.1016/j.devcel.2005.02.014>

Rink, J. C., Gurley, K. A., Elliott, S. A., & Sánchez Alvarado, A. (2009). Planarian Hh signaling regulates regeneration polarity and links Hh pathway evolution to cilia. *Science*, *326*(5958), 1406-1410.

Schuh, M., & Ellenberg, J. (2007). Self-organization of MTOCs replaces centrosome function during acentrosomal spindle assembly in live mouse oocytes. *Cell*, *130*(3), 484-498. <https://doi.org/10.1016/j.cell.2007.06.025>

Shcherbik, N., Pestov, D. G., & Pearson, B. J. (2016). Planarian stem cells sense the identity of the missing pharynx to launch its targeted regeneration. *eLife*, *5*, e14140. <https://doi.org/10.7554/eLife.14140>

Tanenbaum, M. E., Macürek, L., Janssen, A., Geers, E. F., Alvarez-Fernández, M., & Medema, R. H. (2008). Kif15 cooperates with eg5 to promote bipolar spindle assembly. *Current Biology*, *19*(20), 1703-1711. <https://doi.org/10.1016/j.cub.2009.08.027>

Tkemaladze, J. (2023). Cross-senolytic effects of dasatinib and quercetin in humans. *Georgian Scientists*, 5(3), 138-152. doi: <https://doi.org/10.52340/2023.05.03.15>

Tkemaladze, J. (2023). Is the selective accumulation of oldest centrioles in stem cells the main cause of organism ageing?. *Georgian Scientists*, 5(3), 216-235. doi: <https://doi.org/10.52340/2023.05.03.22>

Tkemaladze, J. (2023). Long-Term Differences between Regenerations of Head and Tail Fragments in Schmidtea Mediterranea Ciw4. Available at SSRN 4257823.

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.

Tkemaladze, J. (2023). Structure and possible functions of centriolar RNA with reference to the centriolar hypothesis of differentiation and replicative senescence. *Junior Researchers*, 1(1), 156-170. doi: <https://doi.org/10.52340/2023.01.01.17>

Tkemaladze, J. (2023). The centriolar hypothesis of differentiation and replicative senescence. *Junior Researchers*, 1(1), 123-141. doi: <https://doi.org/10.52340/2023.01.01.15>

Tkemaladze, J. (2024). Absence of centrioles and regenerative potential of planaria. *Georgian Scientists*, 6(4), 59-75. doi: <https://doi.org/10.52340/gi.2024.06.04.08>

Tkemaladze, J. (2024). Cell center and the problem of accumulation of oldest centrioles in stem cells. *Georgian Scientists*, 6(2), 304-322. doi: <https://doi.org/10.52340/gi.2024.06.02.32>

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

Tkemaladze, J. (2024). Elimination of centrioles. *Georgian Scientists*, 6(4), 291-307. doi: <https://doi.org/10.52340/gi.2024.06.04.25>

Tkemaladze, J. (2024). Main causes of intelligence decrease and prospects for treatment. *Georgian Scientists*, 6(2), 425-432. doi: <https://doi.org/10.52340/gi.2024.06.02.44>

Tkemaladze, J. (2024). The rate of stem cell division decreases with age. *Georgian Scientists*, 6(4), 228-242. doi: <https://doi.org/10.52340/gi.2024.06.04.21>

Tkemaladze, J. (2025). Achieving Perpetual Vitality Through Innovation. doi: <http://dx.doi.org/10.13140/RG.2.2.31113.35685>

Tkemaladze, J. (2025). Activated Wheat: The Power of Super Grains. Preprints. doi: <https://doi.org/10.20944/preprints202508.1724.v1>

Tkemaladze, J. (2025). Adaptive Cognitive System Ze. Longevity Horizon, 1(3). doi: <https://doi.org/10.5281/zenodo.15309162>

Tkemaladze, J. (2025). Adaptive Systems and World Models. doi: <http://dx.doi.org/10.13140/RG.2.2.13617.90720>

Tkemaladze, J. (2025). Aging Model - Drosophila Melanogaster. doi: <http://dx.doi.org/10.13140/RG.2.2.16706.49607>

Tkemaladze, J. (2025). Aging Model Based on Drosophila melanogaster: Mechanisms and Perspectives. *Longevity Horizon*, 1(3). doi: <https://doi.org/10.5281/zenodo.14955643>

Tkemaladze, J. (2025). Allotransplantation Between Adult Drosophila of Different Ages and Sexes. doi: <http://dx.doi.org/10.13140/RG.2.2.27711.62884>

Tkemaladze, J. (2025). Anatomy, Biogenesis, and Role in Cell Biology of Centrioles. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14742232>

Tkemaladze, J. (2025). A Novel Integrated Bioprocessing Strategy for the Manufacturing of Shelf-Stable, Nutritionally Upgraded Activated Wheat: Development of a Comprehensive Protocol, In-Depth Nutritional Characterization, and Evaluation of Biofunctional Properties. *Longevity Horizon*, 1(3). DOI:<https://doi.org/10.5281/zenodo.16950787>

Tkemaladze, J. (2025). Anti-Blastomic Substances in the Blood Plasma of Schizophrenia Patients. doi: <http://dx.doi.org/10.13140/RG.2.2.12721.08807>

Tkemaladze, J. (2025). Anti-Blastomic Substances in the Plasma of Schizophrenia Patients: A Dual Role of Complement C4 in Synaptic Pruning and Tumor Suppression. *Longevity Horizon*, 1(3). doi : <https://doi.org/10.5281/zenodo.15042448>

Tkemaladze, J. (2025). Asymmetry in the Inheritance of Centrosomes / Centrioles and Its Consequences. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14837352>

Tkemaladze, J. (2025). A Universal Approach to Curing All Diseases: From Theoretical Foundations to the Prospects of Applying Modern Biotechnologies in Future Medicine. doi: <http://dx.doi.org/10.13140/RG.2.2.24481.11366>

Tkemaladze, J. (2025). Centriole Elimination: A Mechanism for Resetting Entropy in the Cell. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14876013>

Tkemaladze, J. (2025). Centriole Elimination as a Mechanism for Restoring Cellular Order. doi: <http://dx.doi.org/10.13140/RG.2.2.12890.66248/1>

Tkemaladze, J. (2025). Concept to The Alive Language. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14688792>

Tkemaladze, J. (2025). Concept to The Caucasian Bridge. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14689276>

Tkemaladze, J. (2025). Concept to The Curing All Diseases. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14676208>

Tkemaladze, J. (2025). Concept to The Eternal Youth. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14681902>

Tkemaladze, J. (2025). Concept to The Food Security. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14642407>

Tkemaladze, J. (2025). Concept to the Living Space. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14635991>

Tkemaladze, J. (2025). Concept to The Restoring Dogmas. *Longevity Horizon*, 1(1). doi: <https://doi.org/10.5281/zenodo.14708980>

Tkemaladze, J. (2025). Differentiation of Somatic Cells in Multicellular Organisms. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/10.5281/zenodo.14778927>

Tkemaladze, J. (2025). Hypotheses on the Role of Centrioles in Aging Processes. doi: <http://dx.doi.org/10.13140/RG.2.2.15014.02887/1>

Tkemaladze, J. (2025). Induction of germline-like cells (PGCLCs). *Longevity Horizon*, 1(3). doi: <https://doi.org/10.5281/zenodo.16414775>

Tkemaladze, J. (2025). Limits of Cellular Division: The Hayflick Phenomenon. doi: <http://dx.doi.org/10.13140/RG.2.2.25803.30249>

Tkemaladze, J. (2025). Long-Lived Non-Renewable Structures in the Human Body. doi: <http://dx.doi.org/10.13140/RG.2.2.14826.43206>

Tkemaladze, J. (2025). Mechanisms of Learning Through the Actualization of Discrepancies. *Longevity Horizon*, 1(3). doi : <https://doi.org/10.5281/zenodo.15200612>

Tkemaladze, J. (2025). Memorizing an Infinite Stream of Information in a Limited.

Tkemaladze, J. (2025). Memorizing an Infinite Stream of Information in a Limited Memory Space: The Ze Method of a Plastic Counter of Chronotropic Number Frequencies. *Longevity Horizon*, 1(3). doi : <https://doi.org/10.5281/zenodo.15170931>

Tkemaladze, J. (2025). Molecular Insights and Radical Longevity from Ancient Elixirs to Mars Colonies. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14895222>

Tkemaladze, J. (2025). Molecular Mechanisms of Aging and Modern Life Extension Strategies: From Antiquity to Mars Colonization. doi: <http://dx.doi.org/10.13140/RG.2.2.13208.51204>

Tkemaladze, J. (2025). Ontogenetic Permanence of Non-Renewable Biomechanical Configurations in Homo Sapiens Anatomy. *Longevity Horizon*, 1(3). doi : <https://doi.org/10.5281/zenodo.15086387>

Tkemaladze, J. (2025). Pathways of Somatic Cell Specialization in Multicellular Organisms. doi: <http://dx.doi.org/10.13140/RG.2.2.23348.97929/1>

Tkemaladze, J. (2025). Protocol for Transplantation of Healthy Cells Between Adult *Drosophila* of Different Ages and Sexes. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14889948>

Tkemaladze, J. (2025). Replicative Hayflick Limit. *Longevity Horizon*, 1(2). doi: <https://doi.org/10.5281/zenodo.14752664>

Tkemaladze, J. (2025). Solutions to the Living Space Problem to Overcome the Fear of Resurrection from the Dead. doi: <http://dx.doi.org/10.13140/RG.2.2.34655.57768>

Tkemaladze, J. (2025). Strategic Importance of the Caucasian Bridge and Global Power Rivalries. doi: <http://dx.doi.org/10.13140/RG.2.2.19153.03680>

Tkemaladze, J. (2025). Structure, Formation, and Functional Significance of Centrioles in Cellular Biology. doi: <http://dx.doi.org/10.13140/RG.2.2.27441.70245/1>

Tkemaladze, J. (2025). Systemic Resilience and Sustainable Nutritional Paradigms in Anthropogenic Ecosystems. doi: <http://dx.doi.org/10.13140/RG.2.2.18943.32169/1>

Tkemaladze, J. (2025). The Centriolar Theory of Differentiation Explains the Biological Meaning of the.

Tkemaladze, J. (2025). The Centriole Paradox in Planarian Biology: Why Acentriolar Stem Cells Divide and Centriolar Somatic Cells Do Not. Preprints. <https://doi.org/10.20944/preprints202509.0382.v1>

Tkemaladze, J. (2025). The Concept of Data-Driven Automated Governance. *Georgian Scientists*, 6(4), 399–410. doi: <https://doi.org/10.52340/gs.2024.06.04.38>

Tkemaladze, J. (2025). The Epistemological Reconfiguration and Transubstantial Reinterpretation of Eucharistic Practices Established by the Divine Figure of Jesus Christ in Relation to Theological Paradigms. doi: <http://dx.doi.org/10.13140/RG.2.2.28347.73769/1>

Tkemaladze, J. (2025). The Stage of Differentiation Into Mature Gametes During Gametogenesis in Vitro. *Longevity Horizon*, 1(3). doi: <https://doi.org/10.5281/zenodo.16808827>

Tkemaladze, J. (2025). The Tkemaladze Method: A Modernized Caucasian Technology for the Production of Shelf-Stable Activated Wheat with Enhanced Nutritional Properties. *Longevity Horizon*, 1(3). doi: <https://doi.org/10.5281/zenodo.16905079>

Tkemaladze, J. (2025). Through In Vitro Gametogenesis — Young Stem Cells. *Longevity Horizon*, 1(3). doi: <https://doi.org/10.5281/zenodo.15847116>

Tkemaladze, J. (2025). Transforming the psyche with phoneme frequencies "Habere aliam linguam est possidere secundam animam". doi: <http://dx.doi.org/10.13140/RG.2.2.16105.61286>

Tkemaladze, J. (2025). Uneven Centrosome Inheritance and Its Impact on Cell Fate. doi: <http://dx.doi.org/10.13140/RG.2.2.34917.31206>

Tkemaladze, J. (2025). Voynich Manuscript Decryption: A Novel Compression-Based Hypothesis and Computational Framework. Preprints. <https://doi.org/10.20944/preprints202509.0403.v1>

Tkemaladze, J. (2025). Ze World Model with Predicate Actualization and Filtering. doi: <http://dx.doi.org/10.13140/RG.2.2.15218.62407>

Tkemaladze, J. (2025). Ze метод создания пластичного счетчика хронотропных частот чисел бесконечного потока информации. doi: <http://dx.doi.org/10.13140/RG.2.2.29162.43207>

Tkemaladze, J. (2025). Гаметогенез In Vitro: современное состояние, технологии и перспективы применения. Research Gate. <http://dx.doi.org/10.13140/RG.2.2.28647.36000>

Tkemaladze, J., & Apkhazava, D. (2019). Dasatinib and quercetin: short-term simultaneous administration improves physical capacity in human. *J Biomedical Sci*, 8(3), 3.

Tkemaladze, J., & Chichinadze, K. (2005). Potential role of centrioles in determining the morphogenetic status of animal somatic cells. *Cell biology international*, 29(5), 370-374.

Tkemaladze, J., & Chichinadze, K. (2010). Centriole, differentiation, and senescence. *Rejuvenation research*, 13(2-3), 339-342.

Tkemaladze, J., & Gakely, G. (2025). A Novel Biotechnological Approach for the Production of Shelf-Stable, Nutritionally Enhanced Activated Wheat: Protocol Development, Nutritional Profiling, and Bioactivity Assessment. Preprints. <https://doi.org/10.20944/preprints202508.1997.v1>

Tkemaladze, J., & Samanishvili, T. (2024). Mineral ice cream improves recovery of muscle functions after exercise. *Georgian Scientists*, 6(2), 36–50. doi: <https://doi.org/10.52340/gs.2024.06.02.04>

Tkemaladze, J., Tavartkiladze, A., & Chichinadze, K. (2012). Programming and Implementation of Age-Related Changes. In *Senescence*. IntechOpen.

Tkemaladze, J. V., & Chichinadze, K. N. (2005). Centriolar mechanisms of differentiation and replicative aging of higher animal cells. *Biochemistry (Moscow)*, 70, 1288-1303.

Tkemaladze, Jaba and Kipshidze, Mariam, Regeneration Potential of the Schmidtea Mediterranea CIW4 Planarian. Available at SSRN: <https://ssrn.com/abstract=4633202> or <http://dx.doi.org/10.2139/ssrn.4633202>

Vander Heiden, M. G., Cantley, L. C., & Thompson, C. B. (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*, *324*(5930), 1029–1033. <https://doi.org/10.1126/science.1160809>

van Wolfswinkel, J. C., Wagner, D. E., & Reddien, P. W. (2014). Single-cell analysis reveals functionally distinct classes within the planarian stem cell compartment. *Cell Stem Cell*, *15*(3), 326–339. <https://doi.org/10.1016/j.stem.2014.06.007>

Venkei, Z. G., & Yamashita, Y. M. (2018). The centrosome orientation checkpoint is germline stem cell specific and operates prior to the spindle assembly checkpoint in Drosophila testis. *Development*, *145*(14), dev162511. <https://doi.org/10.1242/dev.162511>

Vertii, A., Hehnlly, H., & Doxsey, S. (2016). The centrosome, a multitasking renaissance organelle. *Cold Spring Harbor Perspectives in Biology*, *8*(12), a025049. <https://doi.org/10.1101/cshperspect.a025049>

Vladar, E. K., & Brody, S. L. (2013). Analysis of ciliogenesis in primary culture mouse tracheal epithelial cells. *Methods in Enzymology*, *525*, 285–309. <https://doi.org/10.1016/B978-0-12-397944-5.00014-6>

Wagner, D. E., Wang, I. E., & Reddien, P. W. (2011). Clonogenic neoblasts are pluripotent adult stem cells that underlie planarian regeneration. *Science*, *332*(6031), 811–816. <https://doi.org/10.1126/science.1203983>

Walczak, C. E., Vernos, I., Mitchison, T. J., Karsenti, E., & Heald, R. (1998). A model for the proposed roles of different microtubule-based motor proteins in establishing spindle bipolarity. *Current Biology*, *8*(16), 903–913. [https://doi.org/10.1016/S0960-9822\(07\)00370-3](https://doi.org/10.1016/S0960-9822(07)00370-3)

Wenemoser, D., & Reddien, P. W. (2010). Planarian regeneration involves distinct stem cell responses to wounds and tissue absence. *Developmental Biology*, *344*(2), 979–991. <https://doi.org/10.1016/j.ydbio.2010.06.017>

Witchley, J. N., Mayer, M., Wagner, D. E., Owen, J. H., & Reddien, P. W. (2013). Muscle cells provide instructions for planarian regeneration. *Cell Reports*, *4*(4), 633–641. <https://doi.org/10.1016/j.celrep.2013.07.022>

Woodruff, J. B., Wueseke, O., & Hyman, A. A. (2014). Pericentriolar material structure and dynamics. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *369*(1650), 20130459. <https://doi.org/10.1098/rstb.2013.0459>

Yamashita, Y. M., Mahowald, A. P., Perlin, J. R., & Fuller, M. T. (2007). Asymmetric inheritance of mother versus daughter centrosome in stem cell division. *Science*, *315*(5811), 518–521. <https://doi.org/10.1126/science.1134910>

Zayas, R. M., Hernández, A., Habermann, B., Wang, Y., Stry, J. M., & Newmark, P. A. (2005). The planarian Schmidtea mediterranea as a model for epigenetic germ cell specification: analysis of ESTs from the hermaphroditic strain. *Proceedings of the National Academy of Sciences*, *102*(51), 18491–18496. <https://doi.org/10.1073/pnas.0509507102>

Zhu, S. J., Hallows, S. E., Currie, K. W., Xu, C., & Pearson, B. J. (2015). A mex3 homolog is required for differentiation during planarian stem cell lineage development. *eLife*, *4*, e07025. <https://doi.org/10.7554/eLife.07025>

Прангшвили, А. И., Гаситашвили, З. А., Мацаберидзе, М. И., Чичинадзе, К. Н., Ткемаладзе, Д. В., & Азмайпарашвили, З. А. (2017). К топологии антитеррористических и антикриминальных технологий для образовательных программ. В научном издании представлены материалы Десятой международной научно-технической конференции «Управление развитием крупномасштабных систем (MLSD'2016)» по следующим направлениям: Проблемы управления развитием крупномасштабных систем, включая ТНК, Госхолдинги и Госкорпорации., 284.

Прангшвили, А. И., Гаситашвили, З. А., Мацаберидзе, М. И., Чхартшвили, Л. С., Чичинадзе, К. Н., & Ткемаладзе, Д. В. (2017). & Азмайпарашвили, З. А. (2017). Системные составляющие здравоохранения и инноваций для организации европейской нано-биомедицинской экосистемной технологической платформы. Управление развитием крупномасштабных систем MLSD, 365–368.

Ткемаладзе, Д. (2025). Анатомия, биогенез и роль в клеточной биологии центриолей. doi: [http://dx.doi.org/10.13140.RG.2\(27441.70245\)](http://dx.doi.org/10.13140.RG.2(27441.70245)), 1

Ткемаладзе, Д. (2025). Асимметрия в наследовании центросом/центриолей и ее последствия. doi: [http://dx.doi.org/10.13140.RG.2\(34917.312\)](http://dx.doi.org/10.13140.RG.2(34917.312)), 06.

Ткемаладзе, Д. (2025). Гаметогенез in vitro (IVG) -Этап дифференцировки в зрелые гаметы. <http://dx.doi.org/10.13140/RG.2.2.20429.96482>

Ткемаладзе, Д. (2025). Дифференциация соматических клеток многоклеточных животных. doi: [http://dx.doi.org/10.13140.RG.2\(23348.97929\)](http://dx.doi.org/10.13140.RG.2(23348.97929)), 1.

Ткемаладзе, Д. (2025). Индукция примордиальных клеток, подобных зародышевым клеткам (PGCLCs) современные достижения, механизмы и перспективы применения. <http://dx.doi.org/10.13140/RG.2.2.27152.32004>

Ткемаладзе, Д. (2025). Репликативный Лимит Хейфлика. doi: [http://dx.doi.org/10.13140.RG.2\(25803.302\)](http://dx.doi.org/10.13140.RG.2(25803.302)), 49.

Ткемаладзе, Д. (2025). Элиминация Центриолей: Механизм Обнуления Энтропии в Клетке. doi: [http://dx.doi.org/10.13140.RG.2\(12890.66248\)](http://dx.doi.org/10.13140.RG.2(12890.66248)), 1.

Ткемаладзе, Д., Цомаиа, Г., & Жоржолиани, И. (2001). Создание искусственных самоадаптирующихся систем на основе Теории Прогноза. Искусственный интеллект. УДК 004.89. Искусственный интеллект. УДК 004.89.

Ткемаладзе, Д. В., & Чичинадзе, К. Н. (2005). Центриолярные механизмы дифференцировки и репликативного старения клеток высших животных. Биохимия, 70(11), 1566-1584.

Чичинадзе, К., Ткемаладзе, Д., & Лазарашвили, А. (2012). Новый класс рнк и центросомная гипотеза старения клеток. Успехи геронтологии, 25(1), 23-28.

Чичинадзе, К. Н., & Ткемаладзе, Д. В. (2008). Центросомная гипотеза клеточного старения и дифференциации. Успехи геронтологии, 21(3), 367-371.