Lead Researcher: Cassandra Perera

Assistant Researcher: Ranjeet Sunkara

National Student Research Institution(NSRI)

6/3/2026

The mTOR Signaling Pathway in Cancer: Mechanisms, Therapeutic Strategies, and Emerging Nanotechnology-Based Approaches

Abstract

This literature review will focus on the role of the mechanistic target of rapamycin (mTOR) signaling pathway in normal cellular homeostasis and cancer pathogenesis. The mTOR pathway regulates fundamental cellular functions, including growth, metabolism, protein synthesis, survival, and autophagy. The pathway can be compartmentalized and operates as two separate signaling complexes, mTORC1 and mTORC2, to regulate these distinct processes.

Deregulation of mTOR signaling plays a critical role in tumorigenesis, contributing to cellular proliferation, metabolic reprogramming, and cancer progression in a wide variety of malignancies.

Herein, the established strategies for the therapeutic targeting of the mTOR pathway such as the first-generation rapalogs, the second-generation ATP-competitive inhibitors, and new-generation third-generation inhibitors targeting the resistance against rapalogs, have been reviewed. Limitations for each class of therapies, such as incompletely inhibited pathways, activation of alternative pathways through compensatory feedback, acquired resistance, and toxicities such as nausea, fatigue and immunosuppression have also been summarized. Furthermore, strategies that utilize nanodrug delivery systems to enhance tumor targetability and bioavailability while minimizing drug resistance and toxicity will be discussed. The current review summarizes recent progress in understanding mTOR signaling in cancer, describes the therapeutic potential and limitations of mTOR targeting, and concludes with future perspectives for the improvement of mTOR directed therapies for the cancer treatment.

Keywords: mTOR, cancer, mTORC1, mTORC2, rapalogs, nanoparticles

mTOR Signaling Pathway in Typical Cells

In typical cells, the mechanistic target of rapamycin (mTOR) functions as a serine/threonine kinase and is a critical component of signaling networks that maintain cellular homeostasis. It plays a central role in regulating cell growth, development, and proliferation, as well as key processes such as autophagy (cellular waste removal), metabolism, and apoptosis. The mTOR pathway responds to both extracellular and intracellular cues, enabling the cell to sense changes in its environment and internal energy status. Once activated, mTOR transduces signals to downstream enzymes and

effector proteins, which coordinate and execute the cellular programs required for normal cell function and survival.

mTOR in Cancer Cells

In cancer cells, mTOR signaling is frequently and persistently hyperactivated, enabling continued growth despite signals that would normally slow or halt proliferation. Under these conditions, tumor cells can bypass inhibitory cues such as nutrient stress, energy deprivation, and hypoxia (oxygen deprivation), which typically constrain cell growth in normal tissues. Concurrently, mTOR promotes angiogenesis to increase nutrient and oxygen delivery, ensuring that cancer cells receive sufficient resources to sustain rapid proliferation. Moreover, mTOR suppresses autophagy, reducing programmed self-digestion and thereby supporting the survival and continued expansion of malignant cells.

mTOR Complex Regulatory Mechanisms and Downstream Effects

The mechanistic target of rapamycin (mTOR), a serine/threonine kinase originally named after the immunosuppressive drug rapamycin, plays essential roles in regulating cell growth, proliferation, metabolism, and survival. It functions through two distinct multiprotein complexes, mTORC1 and mTORC2, each with unique biological functions. mTORC1 primarily regulates cell growth by promoting anabolic processes, including protein and lipid synthesis, while suppressing autophagy. In contrast, mTORC2

contributes to cell survival, metabolism, and cytoskeletal organization, thereby regulating cellular structure and morphology. Together, these complexes coordinate growth-related and structural processes that are essential for normal cellular function.

In cancer, additional regulatory mechanisms further modulate mTOR signaling. For example, the mTOR–NEAT1–NONO signaling axis plays a significant role in regulating aerobic glycolysis in hepatocellular carcinoma, demonstrating how mTOR can influence tumor metabolism through multiple pathways. Among the NEAT1 isoforms, only $NEAT1_2$ has been significantly associated with poor prognosis in hepatocellular carcinoma. $NEAT1_2$ organizes nuclear paraspeckles that sequester RNA-binding proteins such as NONO and SFPQ, while mTORC1 suppresses $NEAT1_2$ expression.

mTORC1 activation is tightly regulated at the lysosomal membrane, where it functions as a central sensor of nutrient availability, cellular energy status, and oxygen levels. When amino acids such as leucine and arginine are abundant, sensor proteins including CASTOR1 and Sestrin2 signal through the GATOR1 and GATOR2 complexes to activate Rag GTPases. Activated Rag heterodimers recruit mTORC1 to the lysosomal membrane through interaction with the Raptor subunit, allowing the complex to encounter its direct activator, the small GTPase Rheb. Rheb activity is controlled by the

tuberous sclerosis complex (TSC1/TSC2), which integrates multiple upstream signaling inputs.

Growth factors such as insulin activate the PI3K/Akt and MAPK/ERK pathways, resulting in phosphorylation and inhibition of TSC2. This inhibition maintains Rheb in its active state and promotes mTORC1 activation. Conversely, cellular stressors such as energy deprivation activate AMP-activated protein kinase (AMPK), while hypoxia induces HIF1A and REDD1 expression. Both mechanisms activate TSC2, leading to Rheb inhibition and suppression of mTORC1 signaling.

Activated mTORC1 promotes protein synthesis through two major downstream effectors: p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). S6K1 enhances translation by phosphorylating ribosomal protein S6, eIF4B, and the CAD enzyme involved in nucleotide biosynthesis. In contrast, 4E-BP1 normally suppresses cap-dependent translation by binding eIF4E. Phosphorylation of 4E-BP1 by mTORC1 releases eIF4E, thereby allowing assembly of the translation initiation complex and promoting protein synthesis.

While stimulating anabolic pathways, mTORC1 simultaneously suppresses catabolic processes such as autophagy. It inhibits autophagosome formation through phosphorylation of ULK1 and ATG13 and suppresses lysosomal biogenesis by inhibiting transcription factor EB (TFEB), a master regulator of lysosome formation and autophagic activity.

Unlike mTORC1, mTORC2 is primarily activated by growth factor signaling. It regulates cytoskeletal organization through phosphorylation of protein kinase C alpha (PKCα), ion transport through serum- and glucocorticoid-induced kinase 1 (SGK1), and cell survival through phosphorylation of Akt at Ser473. Through these targets, mTORC2 promotes cell survival, regulates glucose metabolism, and inhibits apoptosis.

Unlike mTORC1, mTORC2 is largely insensitive to rapamycin because its defining subunit, Rictor, sterically hinders access to the FKBP12–rapamycin binding site. Multiple feedback mechanisms further regulate mTOR signaling. For example, activated S6K1 suppresses upstream insulin signaling, creating a negative feedback loop. Furthermore, studies in urothelial carcinoma have demonstrated that 4E-BP1 phosphorylation can, in certain contexts, be directly regulated by PI3K independently of the canonical Akt/mTORC1 pathway, highlighting the complexity and adaptability of mTOR signaling networks.

mTOR as a Therapeutic Target

mTOR is an attractive therapeutic target because the rapid growth and uncontrolled proliferation of many cancer cells are driven, in part, by mTOR hyperactivation. When mTOR signaling is persistently active, tumor cells gain a continuous growth advantage, enabling them to bypass regulatory mechanisms that normally restrain cell division and metabolic activity. This hyperactivation most commonly arises from genetic alterations in upstream regulatory pathways, such as

PI3K/Akt or the TSC complex, which under physiological conditions act to limit mTOR activity. As a result, mTOR remains constitutively active, promoting sustained cell growth, survival, and metabolic reprogramming. Therapeutically targeting mTOR, therefore, represents a rational strategy to disrupt these aberrant signaling processes and reduce the proliferative capacity of cancer cells.

Drugs that Target mTOR: First-Generation Rapalogs

First-generation mTOR inhibitors, commonly referred to as rapalogs, are allosteric agents that primarily target the mTORC1 complex. Rapalogs exert their effects by forming a complex with the intracellular protein FKBP12, which then binds to the FKBP12–rapamycin binding (FRB) domain of mTORC1. This interaction induces a conformational change and creates a steric obstruction that interferes with substrate access to the catalytic site, particularly via the Raptor subunit. The principal substrates affected by this inhibition are S6K1 and 4E-BP1. S6K1 (p70S6 kinase 1) promotes ribosome biogenesis and protein synthesis by activating components of the translational machinery. In cancer, unchecked mTORC1–S6K1 signaling contributes to excessive protein synthesis and rapid tumor growth. S6K1 is highly sensitive to rapalog-mediated inhibition and is strongly suppressed, thereby limiting ribosome production and, consequently, protein synthesis in tumor cells. In contrast, phosphorylation of 4E-BP1 is only partially inhibited by rapalogs, which means that cap-dependent translation is not fully suppressed and can continue to support cancer cell proliferation.

Second-Generation: ATP-Competitive Inhibitors

ATP-competitive inhibitors are the largest class of clinically approved drugs for protein kinases and function by blocking catalytic activity, thereby preventing substrate phosphorylation. However, a key problem is that inhibited kinases may still recognize and bind downstream substrates, thereby acting as scaffolds or binding hubs for signaling partners. It is possible to modulate the allosteric binding cooperativity of a kinase by tuning the chemical nature of the ATP-competitive inhibitor, introducing a new way to fine-tune kinase function. Chemically distinct ATP-competitive inhibitors modulate substrate-binding cooperativity by altering the conformational entropy of the kinase (Olivieri et al.) and shifting the populations of its conformationally excited states. These findings show that binding cooperativity and the enzyme's conformational entropy are correlated. This establishes a new paradigm for the discovery of ATP-competitive inhibitors based on their ability to modulate the allosteric coupling between nucleotide and substrate-binding sites. Overall, ATP-competitive inhibitors reveal that decreased conformational entropy correlates with increased substrate-binding cooperativity (Olivieri et al.).

ATP-competitive inhibitors are the largest class of clinically approved drugs for protein kinases. They function by blocking catalytic activity and preventing substrate phosphorylation. The primary issue with ATP-competitive inhibitors is that inhibited kinases may still recognize and bind downstream substrates, acting as scaffolds or binding sites for signaling partners. The allosteric binding cooperativity of this kinase can be modulated by tuning the chemical nature of the ATP-competitive inhibitor,

offering a new way to fine-tune kinase function (Olivieri et al.). Chemically distinct ATP-competitive inhibitors modulate substrate-binding cooperativity by tuning the kinase's conformational entropy and shifting the populations of its conformationally excited states. The study found that binding cooperativity and the enzyme's conformational entropy are correlated. This is a new paradigm for the discovery of ATP-competitive inhibitors, based on their ability to modulate the allosteric coupling between nucleotide- and substrate-binding sites.

Combination Strategies

Combination strategies for mTOR inhibitors include multiple generations of therapeutics with distinct mechanisms of action. First-generation mTOR inhibitors, known as rapalogues, are allosteric inhibitors that primarily target the mTORC1 complex.[1] These include rapamycin, an antifungal metabolite that binds the FKBP12 protein to allosterically inhibit mTORC1, as well as everolimus, temsirolimus, ridaforolimus, and ABI-009, which are derivatives or analogs used in various cancer-related applications.

Second-generation mTOR inhibitors include ATP-competitive inhibitors that block the catalytic site of both mTORC1 and mTORC2. This group includes mTOR kinase inhibitors (TORKi) such as AZD8055, vistusertib, sapanisertib, and CC-223, as well as dual PI3K/mTOR inhibitors like dactolisib, apitolisib, voxtalisib, and gedatolisib, which are designed to inhibit both PI3K and mTOR to prevent feedback loop activation.[4]

Third-generation mTOR inhibitors help overcome mutations in the FRB domain or kinase domain. Referred to as RapaLinks, these inhibitors are bivalent molecules that

link a first-generation rapalog with a second-generation kinase inhibitor. RapaLinks bind two sites simultaneously by combining the high affinity for the FRB domain of mTORC1 with the effective kinase inhibition of mTOR kinase inhibitor MLN0128 (Yoon et al.). This makes RapaLinks potent against drug-resistant mTOR mutants that are unaffected by previous generations.

Previous Limitations of mTOR drugs

The clinical application of previous generations of mTOR inhibitors has been significantly hindered by biological feedback loops, drug resistance, and severe systemic toxicities. First-generation allosteric inhibitors, or rapalogs, suffer from poor solubility and only partially suppress mTORC1 functions, notably leaving 4E-BP1 phosphorylation modestly inhibited (Mir et al. 16; Zou et al. 483; Yoon 233). A critical limitation of these rapalogs is their tendency to trigger negative oncogenic feedback loops; by inhibiting S6K1, they relieve the suppression of IRS-1, which paradoxically reactivates Akt survival signaling and can promote tumor growth (Mir et al. 16, 20; Tian et al. 483; Zou et al. 617). While second-generation ATP-competitive inhibitors provide a more complete blockade of both mTORC1 and mTORC2, they face challenges including potential off-target effects on related kinases and the inadvertent induction of autophagy, which can promote cancer cell survival (Yoon 236, 249; Mir et al. 18). Furthermore, chronic exposure to these inhibitors frequently leads to the development of drug-resistant mutations, particularly in the kinase or FRB domains, rendering the treatments ineffective over time (Mir et al. 10, 18; Yoon 231, 237). Systemic safety also remains a major hurdle, as these drugs are associated with high rates of adverse events

such as anemia, hyperglycemia, skin rashes, mucositis, and pneumonitis (Mir et al. 22; Yoon 249; Zou et al. 621). Finally, the lack of reliable predictive biomarkers has made it difficult for clinicians to identify which patients will achieve a meaningful response, often resulting in disappointing clinical outcomes despite promising preclinical data (Mir et al. 25; Yoon 249; Tian et al. 485).

Nanoparticle Technology in inhibiting mTOR

Nanoparticle-based drug delivery systems circumvent the primary pharmacokinetic issues around mTOR inhibitors. Lipid-based vesicular drug delivery nanoparticles have been successful, leading to the development of other nanoparticle compositions. These include polymeric micelles, dendrimers, drug conjugates, and polypeptide- and polysaccharide-based nanoparticles (Yoon et al.). The nanoparticles deliver the mTOR-inhibiting drugs, including rapamycin and its rapalogs. This is important, as previously, mTOR therapeutic drugs were nonspecifically distributed and contributed to unwanted downstream effects. Nanoparticle technology can facilitate the precise and controlled autophagy of cancer cells, enhancing the modulation of PI3K/AKT/m-TOR-mediated autophagy and related oncogenic pathways (Rahman). Nanotechnology can also potentially address issues of drug resistance by circumventing those drug-resistance pathways. For instance, the glutathione S-transferase family (GST) is an important example of anti-cancer drug resistance because GST enzymes increase drug resistance in cancer cells by detoxifying anti-cancer drugs, rendering them ineffective. They also inhibit the mitogen-activated protein kinase (MAPK) pathway, which transmits signals from the cell surface to the DNA inside

the nucleus, directing cells to grow, divide, survive, or undergo apoptosis. When this pathway is blocked, it can trigger tumor shrinkage by potentially triggering a self-destruct sequence in many cancer cells. If delivered to the precise cancer cells without being applied to unaffected cells using nanotechnology, this could help treat cancer while helping mitigate side effects to some extent. Currently, gold nanoparticles are being considered for therapeutic use as diagnostic reagents, drug carriers, contrast agents, photothermal agents, and radiosensitizers due to their side- and shape-dependent optical, electrical, and thermal properties. Adverse effects of traditional nanotechnology treatment on normal tissues are avoided in gold nanoparticles due to their high surface area-to-volume ratio and rich surface functionalization chemistry.[16]

Clinical Applications

Previously, the chances of success for nanotechnology remained slim, with the efficiency of injected particles reported to be only 0.7% based on 117 studies from 2006 to 2016 (Torrice et al.). A specific polymeric micellar nanoparticle called Genexol-PM was evaluated in phase II clinical trials and demonstrated non-inferior efficacy as a first-line treatment for ovarian cancer.[14] The clinical application of nanotechnology in delivering mTOR therapeutic drugs—primarily rapalogs like sirolimus and everolimus—is designed to overcome pharmacological barriers such as low water solubility, poor bioavailability, and systemic toxicity. By encapsulating these inhibitors within advanced nanocarriers like albumin-bound nanoparticles (e.g., nab-sirolimus), liposomes, or polymeric micelles, clinicians can achieve targeted delivery to diseased tissues while minimizing off-target effects like immunosuppression. This precision is particularly

transformative in oncology, where formulations like nab-rapamycin exploit the enhanced permeability and retention (EPR) effect to accumulate specifically in tumors, as seen in Phase II clinical trials for advanced solid malignancies. Additionally, in treating autosomal dominant polycystic kidney disease (ADPKD), kidney-targeted micelles are being developed to concentrate drugs at renal cysts, providing sustained-release profiles that improve patient compliance and broaden the therapeutic window for mTOR-based interventions.[21]

Challenges

Developing nanomedicines to target the mTOR pathway appears promising for cancer therapy, but translating this technology to the clinic presents serious roadblocks (Yoon et al.; Rahman). Getting nanoparticles (NPs) to the tumor is incredibly difficult; on average, only 0.7% of the injected dose reaches the target site because the body's immune cells, particularly phagocytic macrophages, tend to clear them rapidly (Torrice et al.). Even when NPs do reach the cells, the precise molecular mechanisms by which they modulate mTOR signaling remain poorly understood (Yoon et al.; Rahman). For example, the long-standing "proton sponge" theory, which suggested that positively charged NPs inhibit mTOR by osmotically damaging lysosomes, has been heavily debated and contradicted by recent studies (Yoon et al.). Furthermore, as soon as NPs enter biological fluids, they get coated in a layer of biomolecules known as a "protein corona." This protein layer can unpredictably strip the NPs of their targeting capabilities, provoke unwanted immune responses, or even promote mTOR activation rather than shut it down (Yoon et al.; El-hefnawy et al.). Finally, there are major safety and toxicity

hurdles to overcome, since some nanomaterials can inadvertently cause severe oxidative stress, degrade lysosomal membranes, and damage healthy cellular structures such as mitochondria and the endoplasmic reticulum (El-hefnawy et al.; Rahman).

Conclusion and Outlook

The complexity of the mTOR signaling network presents both a significant hurdle and a profound opportunity for modern medicine. While its role as a master regulator of cellular growth makes it a primary driver of cancer progression, it also serves as a high-stakes target for the next generation of precision therapies. Moving forward, the shift from broad inhibition to more nuanced control will be essential. Success will likely depend on our ability to leverage sophisticated tools like second-generation inhibitors and targeted delivery systems to bypass the feedback loops and toxicity that have limited earlier treatments. By refining how we modulate the intricate dance between mTOR complexes and their cellular partners, we can move closer to therapies that are not only more potent but also far more selective. Ultimately, the future of oncology lies in our capacity to translate these deep biological insights into clinical tools that can effectively overcome resistance, offering a more hopeful outlook for patients with mTOR-driven diseases.

Works Cited

1. Ali, Eunus S., et al. “Recent Advances and Limitations of MTOR Inhibitors in the Treatment of Cancer.” *Cancer Cell International*, vol. 22, no. 1, Springer Science and Business Media LLC, Sept. 2022, https://doi.org/10.1186/s12935-022-02706-8. Accessed 3 June 2026.

2. Bala, Shashi, and Gyongyi Szabo. “TFEB, a Master Regulator of Lysosome Biogenesis and Autophagy, Is a New Player in Alcoholic Liver Disease.” *Digestive Medicine Research*, vol. 1, AME Publishing Company, 2018, pp. 16–16, https://doi.org/10.21037/dmr.2018.09.03. Accessed 3 June 2026.

3. Beauchamp, E. M., and L. C. Platanias. “The Evolution of the TOR Pathway and Its Role in Cancer.” *Oncogene*, vol. 32, no. 34, Springer Science and Business Media LLC, Dec. 2012, pp. 3923–32, https://doi.org/10.1038/onc.2012.567. Accessed 3 June 2026.

4. Cox, Alysia, et al. “In Vitro Delivery of MTOR Inhibitors by Kidney-Targeted Micelles for Autosomal Dominant Polycystic Kidney Disease.” *SLAS Technology*, vol. 28, no. 4, Elsevier BV, Aug. 2023, pp. 223–29, https://doi.org/10.1016/j.slast.2023.02.001. Accessed 3 June 2026.

5. Durán, Raúl V., and Michael N. Hall. “Regulation of TOR by Small GTPases.” *The EMBO Reports*, vol. 13, no. 2, Springer Science and Business Media LLC, Jan. 2012, pp. 121–28, https://doi.org/10.1038/embor.2011.257. Accessed 3 June 2026.

6. El-hefnawy, Nour-Elhoda, et al. “MTOR Pathway Targeted Inhibition via Rapamycin-Loaded PLGA Nanoparticles for Enhanced Bladder Cancer Therapy.” *Scientific Reports*, vol. 15, no. 1, Springer Science and Business Media LLC, July 2025, https://doi.org/10.1038/s41598-025-06965-z. Accessed 3 June 2026.

7. Gonzalez-Angulo, Ana M., et al. “Weekly *Nab* -Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial.” *Clinical Cancer Research*, vol. 19, no. 19, American Association for Cancer Research (AACR), Oct. 2013, pp. 5474–84, https://doi.org/10.1158/1078-0432.ccr-12-3110. Accessed 3 June 2026.

8. Hay, Nissim, and Nahum Sonenberg. “Upstream and Downstream of MTOR.” *Genes & Development*, vol. 18, no. 16, Cold Spring Harbor Laboratory, Aug. 2004, pp. 1926–45, https://doi.org/10.1101/gad.1212704. Accessed 3 June 2026.

9. Hwang, Duhyeong, et al. “Polymeric Micelles for the Delivery of Poorly Soluble Drugs: From Nanoformulation to Clinical Approval.” *Advanced Drug Delivery Reviews*, vol. 156, Elsevier BV, 2020, pp. 80–118, https://doi.org/10.1016/j.addr.2020.09.009. Accessed 3 June 2026.

10. Lee, Shin-Wha, et al. “An Open-Label, Randomized, Parallel, Phase II Trial to Evaluate the Efficacy and Safety of a Cremophor-Free Polymeric Micelle Formulation of Paclitaxel as First-Line Treatment for Ovarian Cancer: A Korean Gynecologic Oncology Group Study (KGOG-3021).” *Cancer Research and Treatment*, vol. 50, no. 1, Korean Cancer Association, Jan. 2018, pp. 195–203, https://doi.org/10.4143/crt.2016.376. Accessed 3 June 2026.

11. Lunova, Mariia, et al. “Targeting the MTOR Signaling Pathway Utilizing Nanoparticles: A Critical Overview.” *Cancers*, vol. 11, no. 1, MDPI AG, Jan. 2019, p. 82, https://doi.org/10.3390/cancers11010082. Accessed 3 June 2026.

12. Mayer, Ingrid A., and Carlos L. Arteaga. “The PI3K/AKT Pathway as a Target for Cancer Treatment.” *Annual Review of Medicine*, vol. 67, no. 1, Annual Reviews, Jan.

2016, pp. 11–28, https://doi.org/10.1146/annurev-med-062913-051343. Accessed 3 June 2026.

13. “Nanotechnology-Based Targeting of MTOR Signaling in Cancer.” *International Journal of Nanomedicine*, 2020, https://doi.org/10.2147//IJN.S254574. Accessed 3 June 2026.

14. Nawroth, Roman, et al. “S6K1 and 4E-BP1 Are Independent Regulated and Control Cellular Growth in Bladder Cancer.” *PLoS ONE*, edited by Irina Agoulnik, vol. 6, no. 11, Public Library of Science (PLoS), Nov. 2011, p. e27509, https://doi.org/10.1371/journal.pone.0027509. Accessed 3 June 2026.

15. Ning, Limin, et al. “Gold Nanoparticles: Promising Agent to Improve the Diagnosis and Therapy of Cancer.” *Current Drug Metabolism*, vol. 18, no. 11, Bentham Science Publishers Ltd., Jan. 2018, pp. 1055–67, https://doi.org/10.2174/1389200218666170925122513. Accessed 3 June 2026.

16. Olivieri, Cristina, et al. “ATP-Competitive Inhibitors Modulate the Substrate Binding Cooperativity of a Kinase by Altering Its Conformational Entropy.” *Science Advances*, vol. 8, no. 30, American Association for the Advancement of Science (AAAS), July 2022, https://doi.org/10.1126/sciadv.abo0696. Accessed 3 June 2026.

17. Rahman, Md Ataur, et al. “A Comprehensive Review of Nanoparticle-Based Drug Delivery for Modulating PI3K/AKT/MTOR-Mediated Autophagy in Cancer.” *International Journal of Molecular Sciences*, vol. 26, no. 5, MDPI AG, Feb. 2025, p. 1868, https://doi.org/10.3390/ijms26051868. Accessed 3 June 2026.

18. Townsend, Danyelle M., and Kenneth D. Tew. “The Role of Glutathione-S-Transferase in Anti-Cancer Drug Resistance.” *Oncogene*, vol. 22, no. 47, Springer

Science and Business Media LLC, Oct. 2003, pp. 7369–75, https://doi.org/10.1038/sj.onc.1206940. Accessed 3 June 2026.

19. Wagner, Andrew J., et al. “*Nab*-Sirolimus for Patients with Malignant Perivascular Epithelioid Cell Tumors.” *Journal of Clinical Oncology*, vol. 39, no. 33, American Society of Clinical Oncology (ASCO), Nov. 2021, pp. 3660–70, https://doi.org/10.1200/jco.21.01728. Accessed 3 June 2026.

20. Yoon, Mee-Sup. “Nanotechnology-Based Targeting of MTOR Signaling in Cancer.” *International Journal of Nanomedicine*, vol. Volume 15, Informa UK Limited, Aug. 2020, pp. 5767–81, https://doi.org/10.2147/ijn.s254574. Accessed 3 June 2026.

21. Zhang, Hong, et al. “MTOR Regulates Aerobic Glycolysis through NEAT1 and Nuclear Paraspeckle-Mediated Mechanism in Hepatocellular Carcinoma.” *Theranostics*, vol. 12, no. 7, Ivyspring International Publisher, 2022, pp. 3518–33, https://doi.org/10.7150/thno.72581. Accessed 3 June 2026.