Repurposing Antimalarial Lumefantrine for Targeted Therapy in Triple-Negative Breast Cancer

Dipak Rodage
Department of pharmacology, pune university

***Abstract*—Triple-negative breast cancer (TNBC) remains the most aggressive subtype of breast cancer, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Due to the lack of these classical molecular targets, clinical management is heavily reliant on systemic chemotherapy, which suffers from severe off-target toxicities and a high incidence of chemoresistance. The drug repurposing paradigm offers an accelerated, economically viable framework to identify novel oncology indications for well-characterized, FDA-approved non-oncology therapeutics. Lumefantrine, a well-established antimalarial agent, has recently emerged as a promising candidate for oncological repositioning. Preclinical evidence indicates that lumefantrine targets the Friend leukemia integration 1 (Fli-1) transcription factor network, subsequently suppressing downstream effectors including heat shock protein B1 (HSPB1), matrix metalloproteinases (MMPs), and signaling cascades linked to epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) remodeling. Furthermore, lumefantrine acts synergistically with conventional chemotherapeutics to overcome drug resistance and inhibit cell proliferation. This review evaluates the mechanistic foundation, preclinical progress, therapeutic combinations, and formulation hurdles associated with repurposing lumefantrine as a targeted agent in TNBC management.**

I. INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approximately 10% to 20% of all breast cancer cases globally and represents an aggressively metastatic and highly recurrent clinical phenotype (Ávalos-Moreno et al., 2020). By definition, TNBC tumors lack detectable expression of estrogen receptors (ER), progesterone receptors (PR), and amplification of the human epidermal growth factor receptor 2 (HER2) protein (Ávalos-Moreno et al., 2020). This lack of established therapeutic targets renders standard-of-care endocrine regimens and anti-HER2

targeted biologicals completely ineffective, forcing clinical management to rely heavily on cytotoxic chemotherapy, surgical resection, and radiation (Ávalos-Moreno et al., 2020). Despite initial sensitivity to frontline chemotherapy, TNBC exhibits a disproportionately high rate of early recurrence, distal metastasis to visceral organs, and a notably short overall survival window once therapeutic resistance settles in.

The classic drug discovery pipeline represents a grueling, multi-decade process with exorbitant developmental costs and high attrition rates in clinical trials (Ávalos-Moreno et al., 2020). To mitigate these economic and temporal bottlenecks, drug repurposing (or repositioning) has gained profound momentum as a strategy to identify secondary therapeutic indications for clinically approved, well-characterized chemical entities (Ávalos-Moreno et al., 2020). Because repurposed agents have established safety profiles, toxicological thresholds, and pharmacokinetic metrics, their translation into clinical trial phases is highly accelerated (Ávalos-Moreno et al., 2020).

Recently, antimalarial compounds have drawn extensive focus for their off-target anti-neoplastic properties. Among these, the hydrophobic antimalarial lumefantrine has demonstrated potent efficacy in modern oncology screens, revealing unique multi-targeted actions capable of tackling the core survival mechanisms of aggressive malignancies (Rajesh et al., 2020).

II. PHARMACOLOGICAL PROFILE OF LUMEFANTRINE AND ITS ONCO-TARGETS

Historically, lumefantrine has been deployed globally in combination with artemether (as Coartem) for the treatment of uncomplicated Plasmodium falciparum malaria (Duarte & Vale, 2020). While its exact antimalarial mechanism revolves around the inhibition of β-hematin formation into non-toxic hemozoins alongside the disruption of parasitic nucleic acid synthesis, modern high-throughput expression and docking screens have mapped separate molecular interactions in mammalian oncogenic tissue (Duarte & Vale, 2020; Rajesh et al., 2020).

Crucially, modern expression screening revealed that lumefantrine directly binds to and acts as an inhibitor of Friend leukemia integration 1 (Fli-1), an oncogenic transcription factor belonging to the ETS family (Rajesh et al., 2020). In normal physiology, Fli-1 expression is largely restricted to vascular endothelial cells and hematopoietic structures, but its aberrant upregulation has been documented as a core driver across multiple solid tumors, orchestrating cellular transformation, structural evasion, and therapeutic resistance (Rajesh et al., 2020). By establishing a strong chemical interaction with the DNA-binding domain of Fli-1, lumefantrine actively blocks its transcriptional capacity (Rajesh et al., 2020). This primary inhibition yields a cascading down-regulation of downstream target cascades, most notably:

- Heat Shock Protein B1 (HSPB1 / HSP27): A molecular chaperone heavily implicated in preventing apoptosis, maintaining protein homeostasis, and driving cellular resilience under proteotoxic and therapeutic stress (Rajesh et al., 2020).
- EMT Regulators: Key suppression of mesenchymal markers such as Vimentin, Snail, and β-catenin, which typically facilitate metastatic dissemination (Rajesh et al., 2020).

- Extracellular Matrix (ECM) Remodeling Enzymes: Marked down-regulation of Matrix Metalloproteinase-2 (MMP-2) and Matrix Metalloproteinase-9 (MMP-9), limiting structural basement membrane degradation (Rajesh et al., 2020).

III. MECHANISTIC APPLICATION TO TRIPLE-NEGATIVE BREAST CANCER

The molecular profile of TNBC aligns fundamentally with the transcriptional circuits interrupted by lumefantrine. The highly invasive and metastatic nature of TNBC is driven by epithelial-mesenchymal transition (EMT) and constant extracellular matrix remodeling, allowing clusters of cells to break away from the primary tumor and colonize distant tissues (Kamran et al., 2013).

Table 1: Lumefantrine Interventions in Aggressive Cancer Pathways

Molecular Target / Pathway	Mechanism in TNBC Progression	Lumefantrine-Mediated Alteration
Fli-1 Transcription Factor	Overexpressed biomarker driving aggressive cellular phenotypes, tumorigenesis, and stemness.	Directly binds and suppresses transcriptional activity (Rajesh et al., 2020).
HSPB1 (HSP27)	Protects TNBC cells against chemotherapy-induced proteotoxic stress and apoptosis.	Suppressed downstream of Fli-1, inducing apoptotic cascades (Rajesh et al., 2020).
EMT Markers (Vimentin, Snail)	Shifts cells to a migratory mesenchymal state, increasing metastatic potential.	Downregulated, reversing EMT and preserving epithelial architecture (Rajesh et al., 2020).
MMP-2 & MMP-9	Degrades basement membranes, enabling tissue invasion and distal metastasis.	Expression significantly reduced, attenuating invasive capabilities (Rajesh et al., 2020).
Bcl-2 / Bax Ratio	Shifts balance toward anti-apoptotic survival proteins.	Downregulates Bcl-2 while upregulating Bax to promote programmed cell death (Rajesh et al., 2020).

By modifying this network, lumefantrine-mediated therapy induces macro-level phenotypic shifts in aggressive cancer cells. Preclinical assessments show that blocking the Fli-1/HSPB1/EMT axis induces morphological reversion towards a less invasive epithelial phenotype, limits cell-matrix migration, and triggers cell cycle arrest followed by classical

mitochondrial apoptosis, mediated by a significant shift in the Bax/Bcl-2 ratio (Rajesh et al., 2020).

IV. SYNERGISTIC CHEMOTHERAPEUTIC COMBINATIONS

A critical obstacle in treating TNBC is the rapid emergence of multidrug resistance (MDR) against frontline taxanes and anthracyclines (Ávalos-Moreno et al., 2020). Rather than relying entirely on monotherapies, modern translational medicine heavily values combinatory frameworks that utilize antimalarial agents to restore chemotherapeutic sensitivity. Research confirms that lumefantrine exhibits strong synergistic potential when paired with classic antineoplastic drugs like doxorubicin (DOX) and paclitaxel (PTX) on breast cancer lines (Duarte & Vale, 2020).

- Apoptotic Sensitization: By repressing cellular protective mechanisms, such as those governed by heat shock proteins and survival networks, lumefantrine lowers the threshold required for standard cytotoxic drugs to induce cell death (Rajesh et al., 2020).
- Reversal of Efflux-Mediated Resistance: Many antimalarial backbones competitively interact with ATP-binding cassette (ABC) transporters (such as P-glycoprotein), effectively blocking the active efflux of chemotherapeutics out of the malignant cytoplasm, leading to intracellular drug accumulation and heightened cytotoxicity.

V. PHARMACOKINETIC CHALLENGES AND NANO-FORMULATION STRATEGIES

Transitioning lumefantrine from a short-course antimalarial regimen to a sustained oncological targeted therapy presents distinct pharmacological hurdles. Lumefantrine is a highly lipophilic compound characterized by poor and erratic oral bioavailability, heavily dependent on dietary fat intake for optimal systemic absorption. Long-term systemic administration at the higher concentrations required for tumor suppression may also trigger toxicity profiles in off-target metabolic organs like the liver and spleen (Rajesh et al., 2020).

To circumvent these physiological limitations, current engineering paradigms focus heavily on advanced nanomedicine platforms. Novel drug delivery architectures—such as pH-sensitive nano-calcium phosphate lipid nanoparticles (LF-CaP-Ls)—have been developed to optimize lumefantrine delivery (Sethuraman et al., 2021). These nano-enabled carriers exploit the highly acidic extracellular microenvironment of solid tumors, triggering localized, pH-dependent release of the active drug payload (Sethuraman et al., 2021). This targeted approach achieves several critical therapeutic benchmarks:

- It maximizes intracellular drug concentrations within the tumor parenchyma (Sethuraman et al., 2021).
- It prevents systemic toxicity exposure to healthy somatic cells (Sethuraman et al., 2021).
- It bypasses the erratic oral absorption kinetics associated with traditional unformulated dosing routes (Sethuraman et al., 2021).

VI. CONCLUSION AND FUTURE PERSPECTIVES

Repurposing lumefantrine stands out as an innovative, mechanistically grounded approach for establishing targeted therapies within the challenging landscape of triple-negative breast cancer. By acting as a small-molecule inhibitor of the Fli-1 transcription factor and its downstream protective network, lumefantrine selectively targets the exact molecular features—EMT, extracellular matrix degradation, and apoptotic resistance—that make TNBC so lethal. While its synergy with conventional drugs provides a path toward lower chemotherapeutic doses and reduced toxicities, translating these findings into the clinic requires addressing its lipophilic profile. The development of advanced, tumor-targeted nanocarriers will be essential to fully unlock lumefantrine's clinical potential, paving the way for targeted clinical trials that could expand our therapeutic toolkit against TNBC.

REFERENCES

[1] Ávalos-Moreno, M., López-Tejada, A., Blaya-Cánovas, J. L., Cara-Lupiañez, F. E., González-González, A., Lorente, J. A., Sánchez-Rovira, P., & Granados-Principal, S. (2020). Drug Repurposing for Triple-Negative Breast Cancer. Journal of Personalized Medicine, 10(4), 200. https://doi.org/10.3390/jpm10040200

[2] Duarte, D., & Vale, N. (2020). New Trends for Antimalarial Drugs: Synergism between Antineoplastics and Antimalarials on Breast Cancer Cells. Biomolecules, 10(12), 1623. https://doi.org/10.3390/biom10121623

[3] Kamran, M. Z., Patil, P., & Gude, R. P. (2013). Role of STAT3 in Cancer Metastasis and Translational Advances. BioMed Research International, 2013, 1–15. https://doi.org/10.1155/2013/421821

[4] Rajesh, Y., Biswas, A., Kumar, U., Banerjee, I., Das, S., Maji, S., Das, S. K., Emdad, L., Cavenee, W. K., Mandal, M., & Fisher, P. B. (2020). Lumefantrine, an antimalarial drug, reverses radiation and temozolomide resistance in glioblastoma. Proceedings of the National Academy of Sciences, 117(22), 12324–12331. https://doi.org/10.1073/pnas.1921531117

[5] Sethuraman, V., Janakiraman, K., Krishnaswami, V., Natesan, S., & Kandasamy, R. (2021). In vivo synergistic anti-tumor effect of lumefantrine combined with pH responsive behavior of nano calcium phosphate based lipid nanoparticles on lung cancer. European Journal of Pharmaceutical Sciences, 158, 105657. https://doi.org/10.1016/j.ejps.2020.105657