



Chrono-Adaptive Resistance Disruption (CARD): A Novel Pharmacological Framework to Address Anticancer Drug Resistance

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Abstract

Drug resistance in anticancer therapy has long been a major challenge in oncology, biomedical, and pharmacological research. Despite numerous efforts targeting molecular and pathway-level mechanisms and evaluating combination therapies, current pharmacological approaches remain largely stagnant and show limited consideration of circadian variations in tumor biology and drug resistance. Growing preclinical and clinical evidence suggests that circadian rhythms fundamentally regulate drug metabolism, cellular stress, DNA repair, and adaptive resistance mechanisms. This article introduces the Chrono-Adaptive Resistance Disruption (CARD) framework and proposes a novel therapeutic strategy leveraging circadian biology to overcome anticancer drug resistance. Unlike conventional chronotherapy or resistance management approaches, CARD actively disrupts resistance trajectories using time-optimized drug regimens and adaptive pharmacological interventions. It provides a comprehensive biological framework supported by extensive preclinical and clinical evidence reported in the biomedical and pharmacological literature. To date, this combined strategy has not been systematically conceptualized as an integrated framework in biomedical and pharmacological literature, highlighting the novelty and translational relevance of CARD.

Keywords:

resistance to anticancer drugs; chrono pharmacology; circadian rhythm; adaptive resistance; pharmacodynamics; chrono adaptive resistance disruption

1. Introduction

Anticancer pharmacotherapeutic agents, including targeted therapies, antibody-drug conjugates, immune checkpoint inhibitors, and precision-guided small molecules, have significantly transformed the treatment of cancer [1]. Despite these therapeutic advancements, drug resistance is currently recognized as the principal cause of treatment failure, tumor recurrence, tumor metastasis, and cancer-related mortality [2]. From a biomedical and pharmacological perspective, drug resistance is now recognized not merely as a result of persistent genomic mutations, but as a dynamic, adaptive process involving time-dependent vari-

ations in intracellular signaling, pharmacokinetics, tumor metabolism, DNA repair, and phenotypic plasticity [3].

Recent advances in circadian oncology have revealed that tumor cells contain dysregulated yet functional molecular clocks involving the CLOCK, BMAL1, PER, and CRY proteins, which regulate transcriptional oscillatory programs controlling the cell cycle, apoptosis, oxidative stress, autophagy, immune surveillance, and xenobiotic metabolism [4]. These oscillations directly regulate drug absorption, intracellular drug exposure, drug-target engagement, DNA damage accumulation, and repair kinetics [5]. Therefore, the pharmacodynamic sensitivity of

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tumor cells to cytotoxic, targeted, and immunotherapeutic agents may be significantly modulated according to the circadian timing of drug administration [6].

The conventional dosage regimens of chemotherapeutic agents have been standardized primarily according to chronological time, largely disregarding biological temporal heterogeneity between host and tumor cells [7]. Such static dosing strategies may inadvertently expose tumor cells during periods of reduced susceptibility while simultaneously facilitating adaptive survival pathway activation during post-treatment recovery [8]. Recent studies underscore the importance of temporal alignment between the dosing regimens of chemotherapeutic agents and circadian vulnerability phases. A lack of such temporal concordance has been linked to the emergence of reversible drug-tolerant persister states, altered ATP-binding cassette (ABC) transporter expression, enhanced DNA repair, and metabolic reprogramming as compensatory survival mechanisms [9]. The relevance of the circadian timing system has been emphasized in breast cancer and glioblastoma, where circadian disruption is implicated in endocrine resistance, ABCB1-mediated efflux, temozolomide tolerance, maintenance of cancer stem-like phenotypes, and DNA repair activation [10,11]. In breast cancer, BMAL1 and PER2 expression has been implicated in the modulation of estrogen receptor expression, thereby contributing to the development of endocrine resistance. In glioblastoma, circadian regulation of DNA

repair enzymes and tumor stem-cell cycling has been shown to influence the therapeutic efficacy of chemotherapeutic agents, including alkylating agents and kinase inhibitors [11].

While chronotherapy traditionally administers chemotherapy at times when tumors are presumed most susceptible, aiming to minimize toxicity; however, no unifying framework currently exists to systematically exploit biological timing to prevent or disrupt therapeutic resistance [12]. To address this gap, the concept of Chrono-Adaptive Resistance Disruption (CARD) has been developed. This framework is based on the integration of circadian vulnerability mapping, adaptive resistance surveillance, and chrono-sequential therapeutic interventions [13]. CARD introduces the concept of time as a critical variable in the development of pharmacological strategies aimed at disrupting chemotherapy-induced resistance. This approach is based on the principle of intervening during the reversible early adaptive resistance phase, contrasting with conventional chemotherapy resistance paradigms that are largely reactive of therapeutic failure [14]. This perspective article aims to establish the biological rationale, pharmacological mechanisms, clinical relevance, and potential translational implications underlying the development of Chrono-Adaptive Resistance Disruption (CARD) (see Figure 1), a novel framework for the disruption of chemotherapy-induced resistance.

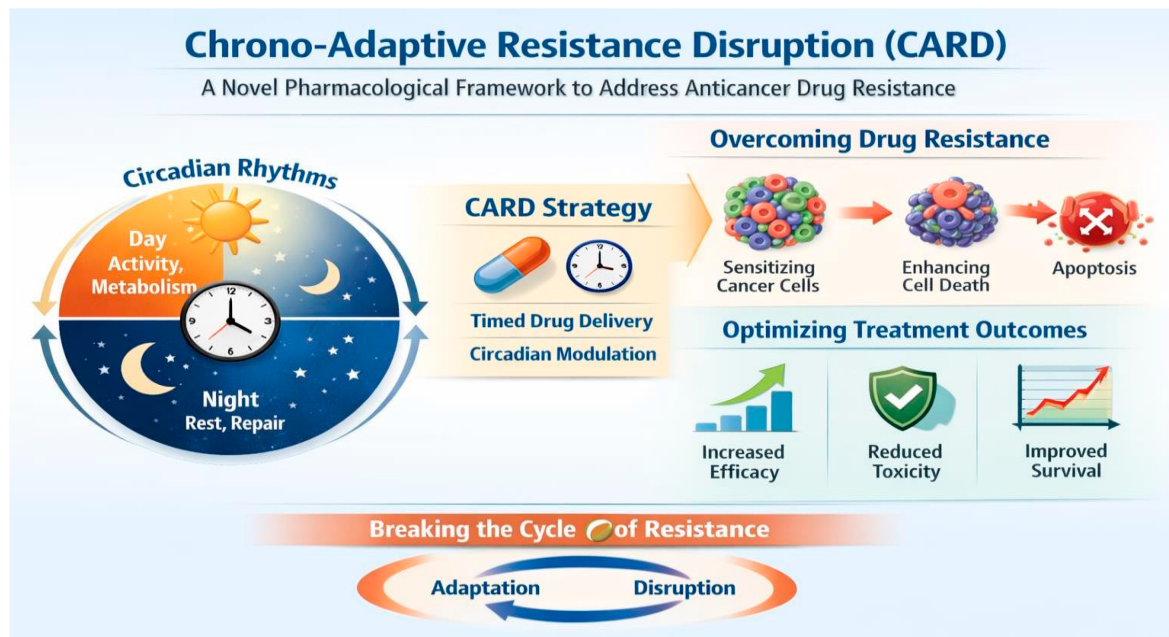


Figure 1: Chrono-Adaptive Resistance Disruption (CARD).

2. Pharmacological Mechanisms Underlying Anticancer Drug Resistance

2.1. Target-Based and Pathway-Mediated Resistance

Resistant cells may arise from intrinsic alterations in therapeutic targets, compensatory signaling pathway activation, and regulatory feedback reprogramming of regulatory feedback circuits [15]. Point mutations in kinase domains, overexpression of the therapeutic target, and mechanisms that bypass downstream signaling pathways collectively reduce drug efficacy by altering its pharmacodynamic profile [16]. From a chronopharmacological perspective, the functional state of signaling pathways is not constant; rather, it exhibits circadian oscillatory dynamics. Consequently, the efficiency of drug–target interactions becomes inherently time-dependent [17].

2.2. Drug Transport, Metabolism, and Circadian Regulation

Drug transport, drug metabolism, and circadian rhythm regulation all contribute significantly to resistance in anticancer therapy. The first mechanism is associated with alterations in transmembrane transport pathways in cancer cells [18]. This mechanism involves the upregulation of membrane transport proteins responsible for the active efflux of anticancer agents from tumor cells, thereby reducing intracellular drug accumulation and promoting drug elimination. Such efflux transporters include P-glycoprotein (P-gp) and multidrug resistance–associated proteins (MRPs), among others. Elevated expression of ATP-binding cassette (ABC) transporters has been consistently associated with the development of multidrug resistance across multiple cancer types [19]. The second mechanism pertains to the enhanced activity of enzymes involved in the biotransformation of anticancer agents within the body. In particular, this includes upregulated expression and increased functional activity of cytochrome P450 enzymes (CYP450 family). Consequently, augmented metabolic processing leads to accelerated conversion of drugs into inactive metabolites, thereby reducing therapeutic efficacy [20]. Furthermore, variations in Phase II metabolic enzymes may enhance detoxification capacity and, consequently, increase protection of tumor cells against the cytotoxic effects of anticancer agents. With regard to circadian rhythm regulation, the circadian clock modulates daily oscillatory gene expression in drug transport, metabolism, and DNA repair, contributing to time-dependent therapeutic responses [21]. Disturbance

in circadian rhythm regulation may result in dysregulated functioning of drug transport and metabolic pathways, thereby contributing to reduced therapeutic efficacy. A growing understanding of the role of chronobiology in pharmacokinetics and pharmacodynamics has given rise to the concept of chronotherapy, defined as the administration of therapeutic agents in alignment with endogenous biological rhythms to optimize efficacy and minimize toxicity [22].

2.3. Adaptive Drug Tolerance and Pharmacological Plasticity

Adaptive drug tolerance is a state of transient, reversible survival of cancer cells under lethal drug concentrations, without permanent genetic mutations conferring stable resistance [23]. This state is mechanistically characterized by chromatin remodeling, epigenetic plasticity, metabolic downregulation, enhanced oxidative stress buffering, activation of autophagy pathways, and engagement of the unfolded protein response (UPR) signaling cascade [24]. Drug-tolerant persister cells represent an optimal therapeutic target for cancer treatment. In breast cancer, the emergence of adaptive resistance to endocrine therapies and CDK4/6 inhibitors is associated with circadian dysregulation of the estrogen receptor, PER2 downregulation, and oscillatory ABC transporter expression of ATP-binding cassette (ABC) transporters [25]. In glioblastoma, circadian regulation of DNA repair enzymes, including O6-methylguanine-DNA methyltransferase (MGMT) and components of the mismatch repair system, may significantly influence sensitivity to temozolomide [26]. Circadian variation in the proliferation and stress adaptation dynamics of tumor stem-like cells generates a pharmacologically exploitable temporal window of vulnerability [27]. Chrono-Adaptive Resistance Disruption (CARD) specifically targets this transient temporal adaptive state of cancer cells prior to the establishment of stable, clonal drug-resistant populations.

3. Circadian Biology in Biomedical and Pharmacological Contexts

Circadian rhythm disruption plays a significant role in the development of resistance to anticancer therapies across multiple cancer types. In breast cancer, BMAL1 and PER2 are implicated in the regulation of hormonal signaling and drug transport processes, where resistance arises in part through ABCB1-mediated drug efflux and endocrine escape mechanisms. These alterations reduce the therapeutic efficacy of agents such as tamoxifen and doxorubicin, thereby limiting their clinical benefit. In

this context, the importance of appropriate sequencing and temporal optimization of endocrine therapies remains critically important [28]. In glioblastoma, the CLOCK and CRY genes regulate DNA repair processes, and resistance to temozolomide has been associated with increased MGMT-mediated DNA repair activity. These findings emphasize the importance of temporal regulation of DNA repair in optimizing chemotherapy administration [29]. In colorectal cancer, PER1 expression has been

implicated in modulating resistance development through escape from apoptosis, thereby reducing the cytotoxic efficacy of agents such as oxaliplatin. These observations further support the rationale for time-specific drug infusion strategies to enhance therapeutic outcomes. Similarly, in lung cancer, disruption of BMAL1 has been associated with altered EGFR signaling adaptation and bypass mechanisms, ultimately diminishing the effectiveness of tyrosine kinase inhibitors (TKIs) [30] (Table 1).

Table 1: Recent literature linking circadian rhythm with cancer drug resistance mechanisms.

Cancer Type	Circadian Target	Resistance Mechanism	Drug Class	CARD Relevance
Breast Cancer	BMAL1/PER2	ABCB1 Efflux, Endocrine Escape	Tamoxifen, Doxorubicin	Endocrine Sequencing
Glioblastoma	CLOCK/CRY	MGMT-Mediated DNA Repair	Temozolomide	DNA Repair Vulnerability Targeting
Colorectal Cancer	PER1	Apoptosis Escape	Oxaliplatin	Chrono-Modulated Infusion
Lung Cancer	BMAL1	EGFR Adaptive Bypass	TKIs	Timed Kinase Inhibition

3.1. Chrono-Adaptive Resistance Disruption (CARD)-A Novel Pharmacological Strategy

3.1.1. Definition & Conceptual Innovation

Chrono-Adaptive Resistance Disruption (CARD) may therefore be defined as a pharmacologically driven, time-dependent strategy that seeks to synchronize the administration of antitumor agents with circadian windows of tumor vulnerability, while concurrently disrupting adaptive resistance mechanisms in a dynamic and temporally regulated manner [31]. The underlying principle of Chrono-Adaptive Resistance Disruption (CARD) distinguishes it from conventional therapeutic approaches, as it shifts the focus from post-clinical failure intervention to proactive prevention of therapeutic resistance.

4. Methodological Framework for CARD in Biomedical and Pharmacology Research

4.1. Temporal Pharmacodynamics Profile

CARD is preceded by a comprehensive temporal characterization of drug response profiles. Pharmacodynamic probes assessing target inhibition, DNA damage accumulation, and apoptotic induction may be employed to delineate time-dependent resistance signatures within tumors. This represents a departure from conventional

dose–response methodologies, which are typically conducted at arbitrary and non-physiological time points, thereby failing to capture the dynamic, time-dependent nature of drug sensitivity and resistance.

4.2. Adaptive Resistance Monitoring and Pharmacological Interception

Longitudinal monitoring of molecular and pharmacological resistance phenotypes—including circulating tumor DNA, transcriptional stress signatures, and metabolic profiles—enables the early identification of emerging adaptive resistance trajectories. Chrono-Adaptive Resistance Disruption (CARD) proposes a pre-emptive pharmacological strategy, the optimization of which in terms of dosing timing and sequential administration prior to the establishment of stable resistance remains not yet standardized in biomedical and pharmacological practice (see Figure 2).

4.3. Chrono-Sequential Drug

Instead of continuous drug administration, Chrono-Adaptive Resistance Disruption (CARD) employs chrono-sequential drug delivery, whereby distinct pharmacological classes are administered at specific circadian time points optimized for their respective mechanisms of action. Cytotoxic agents, targeted therapies, and epigenetic modulators are precisely temporally coordinated to disrupt resistance-associated signaling networks. This approach represents a novel and largely unestablished paradigm within contemporary pharmacological therapy.

Adaptive Resistance Monitoring & Pharmacological Interception

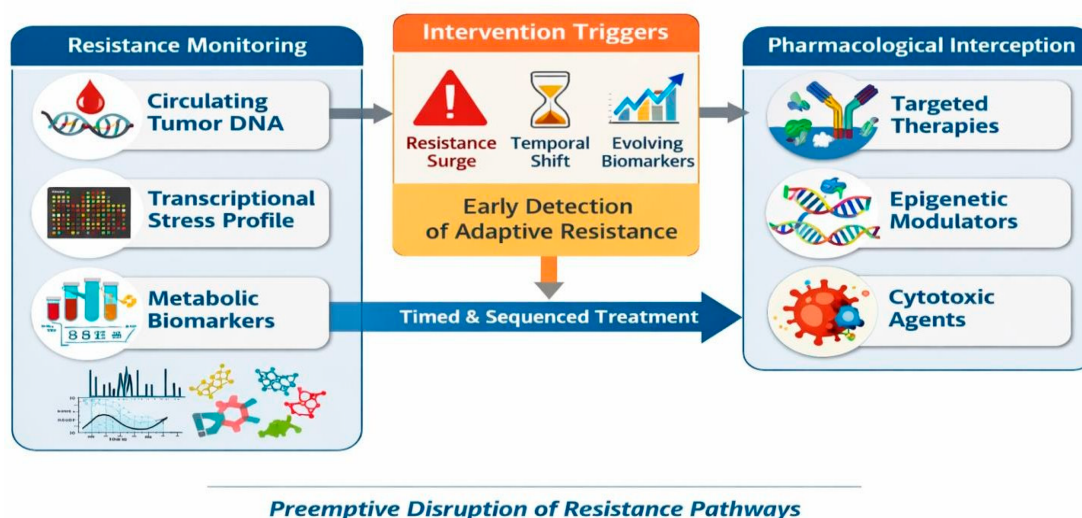


Figure 2: Adaptive resistance monitoring and pharmacological interception.

4.4. Systems Pharmacology and Predictive Modeling

CARD integrates systems pharmacology frameworks with machine learning methodologies, enabling the prediction of drug resistance evolution under varying temporal conditions. This approach conceptualizes time as a fundamental pharmacological parameter that can be quantitatively leveraged for predictive modeling, with the aim of optimizing drug administration schedules and improving therapeutic outcomes.

5. Clinical and Translational Implications of the CARD System

The CARD system is highly aligned with the objectives of biomedical and pharmacological research, as it integrates molecular mechanisms, drug actions, and clinical applications within a unified framework. The implementation of CARD may facilitate the development of adaptive clinical trial designs, chronopharmacological dosing schedules, and resistance-informed therapeutic guidelines. Emerging paradigms, particularly in digital health monitoring and non-invasive biomarker assessment, further strengthen the conceptual and translational foundation of CARD-based therapeutic strategies.

6. Conclusions

Chrono-Adaptive Resistance Disruption (CARD) represents a novel pharmacological paradigm in which

cancer drug resistance is conceptualized as a time-dependent, potentially programmable biological process, rather than an inevitable end-stage consequence of prolonged chemotherapy. By integrating the principles of circadian biology, temporal pharmacodynamics, adaptive monitoring of anticancer drug resistance, and systems pharmacology, the Chrono-Adaptive Resistance Disruption (CARD) model represents a novel therapeutic paradigm in which the prevention of chemotherapy-induced resistance is established as a primary objective of cancer treatment. Emerging evidence from breast cancer and glioblastoma models provides substantial support for the plausibility of this hypothesis. The integration of literature-supported circadian mechanisms underlying cancer drug resistance, together with emerging clinical evidence in chronotherapy, further strengthens this conceptual framework. Although additional empirical validation is required to substantiate the hypothesis, the Chrono-Adaptive Resistance Disruption (CARD) model represents a promising and conceptually robust paradigm for the future design of clinical trials in cancer chemotherapy.

List of Abbreviations

ABC	ATP-Binding Cassette
ABCB1	ATP-Binding Cassette Subfamily B Member 1
BMAL1	Brain and Muscle ARNT-Like 1
CARD	Chrono-Adaptive Resistance Disruption
CLOCK	Circadian Locomotor Output Cycles Kaput
CRY	Cryptochrome

CYP450	Cytochrome P450 Enzymes
DNA	Deoxyribonucleic Acid
MGMT	O6-Methylguanine-DNA Methyltransferase
mRNA	Messenger Ribonucleic Acid
MRP	Multidrug Resistance–Associated Proteins
PD	Pharmacodynamics
PER	Period Proteins
P-gp	P-glycoprotein
RNA	Ribonucleic Acid
TKI	Tyrosine Kinase Inhibitors
UPR	Unfolded Protein Response

Author Contributions

Conceptualization: S.S.S.; Methodology: S.S.R.; Investigation: A.M.M.; Supervision: B.S.; Validation: B.S.; Writing—original draft: S.S.S., Visualization: S.S.S., A.M.M. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

AI tool (ChatGPT) was used only for language editing and rephrasing to improve clarity. The authors take full responsibility for all content.

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