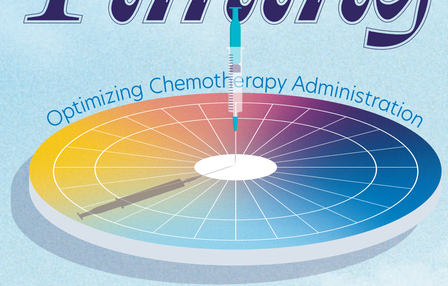
It's All in the Timing



Conceptualizing Chronotherapy in Medicine

Life on this planet revolves around sunlight. Most animals have evolved an internal time-keeping device— the circadian or biological clock— to adapt to daily changes in light (day-night) and seasonal cycles. The biological clock synchronizes light with other environmental signals, such as temperature and food intake throughout the day, and controls an animal's physiology, metabolism, and behavior. The cellular and biochemical signals triggered by the clock help animals adapt to their ever-changing environments. Consequently, perturbations in the circadian clock contribute to numerous human diseases, such as insomnia and other sleep disturbances, cardiovascular diseases, stroke, hypertension, diabetes, neurological and psychiatric illnesses, and cancer.

Clock-mediated daily oscillations in cellular metabolism and energy consumption directly influence pharmaceutical drug biotransformation. The timing of drug metabolism and detoxification determines a compound's safety and efficacy. Incorporating chronotherapy, where drug administration occurs at a specific time of day, maximizes efficacy and diminishes toxicity, improving clinical outcomes in many diseases, including cancer.[1]

Written by Sejal Davla, PhD | Designed by Jen Power, MSc

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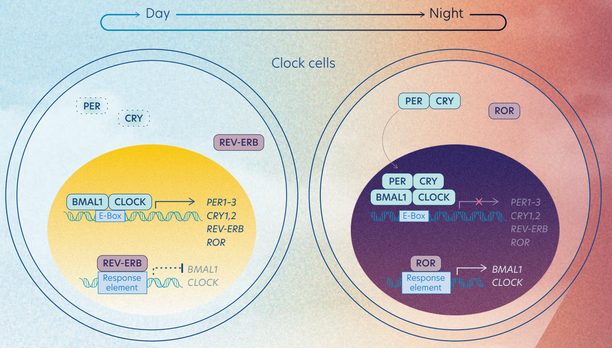
The Cogs and Gears of the Circadian Clock

Clock genes generate and maintain daily circadian rhythms. The core clock machinery consists of four genes in mammals: brain-muscle-aryl hydrocarbon receptor nuclear translocator-like protein 1 (*Bmal1*), circadian locomotor output cycles kaput (*Clock*), period (*Per*), and cryptochrome (*Cry*). Together, they operate in a transcription/translation feedback loop (TTFL) to achieve a precise 24-hour period.

BMAL1 and **CLOCK** proteins function during the day. At night, **PER** and **CRY** proteins dimerize in the cytoplasm and translocate to the nucleus, inhibiting *Bmal1* and *Clock* transcription. Sunlight degrades the PER/CRY complex, which resumes *Clock* and *Bmal1* transcription and results in a new 24-hour cycle. The retinoic acid receptor-related orphan receptor (**ROR**) and the nuclear receptor **REV-ERB** proteins provide robustness to the rhythm generated by the *Bmal1* gene.[2]



Most organs such as the heart, liver, and intestine have an active circadian TTFL machinery and generate their own daily cellular oscillations. The clock cells in the suprachiasmatic nucleus (**SCN**) brain region synchronize all the other bodily clocks. The SCN receives direct inputs from the eyes and incorporates changes in light intensity to run and reset the clock.[2]

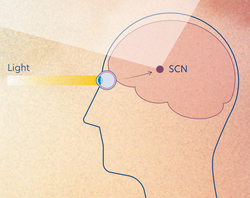
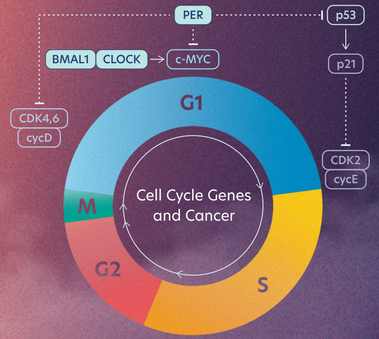
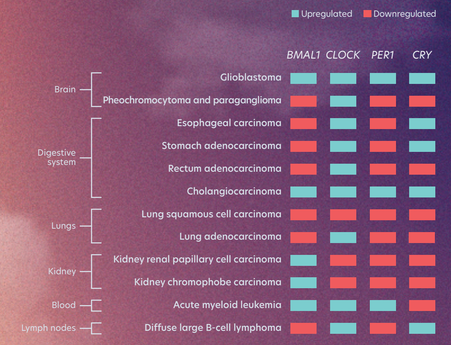


Image adapted from Bermúdez-Guzmán et al.[3]



The Interplay Between Clock and Cancer Genes

The clock genes coordinate the rhythmic expression of clock-controlled genes (CCGs) that maintain tissue homeostasis, metabolism, cell division, and apoptosis. A slew of CCGs are cell cycle regulators that contribute to cancer initiation and progression. For example, the clock controls proto-oncogenes **c-MYC** and **cycD** and tumor suppressor gene **p53**. In addition, the CCGs in cancer metabolic pathways determine rate-limiting enzyme activities and cell surface molecule expression which are often cancer treatment targets.[2]



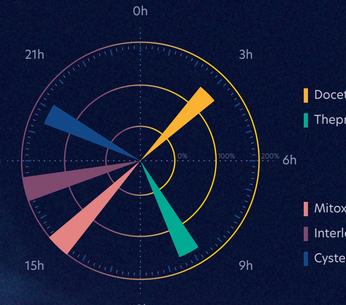
Data compiled from Zhou et al.[4]

Clocks in Cancer

Circadian clock gene expression in cancer cells varies throughout the tumor microenvironment. Clock gene disruptions in tumor cells are key hallmarks associated with cancer initiation and tumor formation.[4]

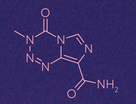
Circadian Regulation of Anticancer Drugs

Applications of chronobiology in medicine remain at the fringes of clinical practice and drug discovery. Circadian timing influences the pharmacokinetics, tolerability, and effectiveness of several anticancer drug classes.[1] The data from Lévi et al. demonstrates the improvements in anticancer drug tolerability at a given drug administration time in preclinical mouse models.[5] The diagram on the right illustrates circadian timing where animals were kept in light from 0–12 hours and darkness from 12–24 hours and relative magnitude of survival benefit at a given time, from 0 to 200 percent.

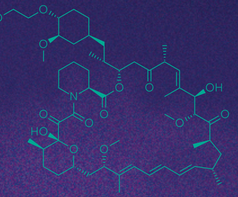


Successful Chrono-chemotherapy Trials

Administering a therapy when a drug target is abundant and drug absorption and metabolism are at their peak is at the heart of chronotherapy. Only 0.15 percent of the currently registered cancer clinical trials include a form of circadian intervention.[5] Many ongoing trials are for various breast neoplasms and bone, brain, and colorectal tumors.



Temozolomide (TMZ) is a standard chemotherapy drug for glioblastoma. Patients taking morning TMZ showed longer overall survival compared to patients on an evening drug administration schedule.[6]



Everolimus (EV) is a chemotherapeutic agent used for breast, lung, and pancreas cancers to block tumor growth. EV mainly targets mTOR, whose activity is under the control of the circadian clock. Morning administration of EV in metastatic breast cancer patients improved drug tolerability, minimized metabolic alterations, and decreased fatigue compared to patients who took EV in the evening.[7]

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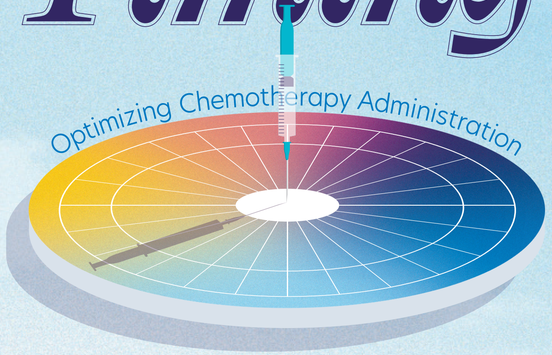

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