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Opinion

Time-of-day dependency of adoptive cell therapies

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Adoptive cell therapies (ACTs), such as chimeric antigen receptor (CAR)-T cell therapy, have revolutionized cancer treatment, especially for hematological cancers. However, patient responses vary considerably. Emerging research reveals a striking influence of time of day (ToD) on ACT efficacy. Administering ACT during the early behavioral active phase enhances tumor control and reduces toxicity in preclinical models, an effect linked to the circadian clock. Latest clinical data also point to ToD effects in the cancer setting. In this opinion article we explore current insights and discuss the emerging underlying mechanisms. We propose that integrating ToD into clinical practice could represent a powerful yet easily implementable therapeutic regimen to improve efficacy and safety of ACT.

Highlights

The tumor vasculature and adoptively transferred T cells express adhesion and chemokine receptors in a rhythmic fashion that strongly impacts T cell tumor infiltration.

Circadian control over T cell activation and phenotype may contribute to the antitumor response of adoptive cell therapies performed in the clinic.

Timing adoptive cell therapy delivery to align with circadian rhythms at the early behavioral active phase may improve tumor control and reduce adverse effects in the clinic.

Current landscape of ACTs

In the mid-20th century, researchers demonstrated that transferring lymphoid cells from an immunized donor to a recipient conferred immunity in the latter, coining the term 'adoptive immunity' and laying the foundation for what we now call ACT [1,2]. ACT broadly refers to the therapeutic transfer of leukocytes to mount disease-specific immune responses [3]. Advances in cellular engineering and immunotherapy have led to the development of four clinically approved ACT modalities for cancer treatment [3]: (i) transfer of tumor-infiltrating lymphocytes (TILs) to amplify naturally occurring tumor-reactive T cells [4]; (ii) transfer of virus-specific allogenic T cells, selected on partial major histocompatibility complex (MHC) compatibility, to restore antiviral immunity against virus-driven malignancies [5].;(iii) transfer of T cell receptor (TCR)-engineered T cells that recognize tumor-associated antigens presented on MHC molecules [6]; and (iv) transfer of CAR-T cells expressing synthetic receptors that target tumor surface 'self' antigens, bypassing MHC restrictions [7].

The introduction of CAR-T cell therapy in 2017 marked a paradigm shift in ACT, significantly improving outcomes of patients with relapsed/refractory B cell and plasma cell malignancies [8,9]. CAR-T therapy builds upon earlier insights from TIL therapy developed for advanced melanoma. TIL therapy involves harvesting TILs from a patient's tumor, expanding them *ex vivo*, and reinfusing them to improve antitumor responses [4,10]. Similarly, CAR-T cell therapy involves collecting T cells from patient's blood, genetically engineering them to express a CAR, then expanding and reinfusing them [11]. Following reinfusion, these adoptively transferred T cells persist in the patient for weeks to years, depending on the specific product [12–14].

While ACT has transformed cancer treatment, significant challenges remain, including limited persistence, poor infiltration into solid tumors, and the functional exhaustion of transferred cells [15]. Here, we discuss emerging preclinical evidence that indicates ToD to be a novel factor potentially influencing ACT efficacy.

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The circadian clock

The circadian clock is an internal timekeeping system, present in virtually all mammalian cells, to anticipate and adapt to daily environmental changes. It operates on a 24 h cycle, driven by a transcription–translation feedback loop (TTFL) of core clock genes [16]. At the heart of the TTFL is the transcription factor **BMAL1** (see Glossary), which forms a heterodimer with CLOCK to activate the transcription of *PER* and *CRY* genes. The resulting PER and CRY proteins translocate to the nucleus and inhibit BMAL1/CLOCK transcriptional activity, creating a negative feedback loop that sustains **circadian rhythms** [17]. Additional regulators such as REV-ERBs, RORs, and DBP fine-tune the system by modulating *BMAL1* expression [16]. Although the TTFL operates autonomously within cells, it is synchronized across the organism by the **suprachiasmatic nucleus (SCN)** within the brain, known as the central clock. The central clock aligns the TTFL with the external environment, using cues such as light, food intake, and temperature [18]. This partitions the day into phases of behavioral activity and rest. In nocturnal rodents, which are generally employed as preclinical models, behavioral activity occurs during the night; in humans, it takes place during the day. These differences need to be kept in mind when discussing results and aiming to translate preclinical research findings into the clinic. We refer here to behavioral active and rest phases, rather than night and day, when discussing findings across species, to be able to more easily compare mouse and human data.

Circadian rhythms in tissue infiltration of leukocytes

Over the past decade it has become clear that the immune system follows a strong ~24 h circadian cycle, with many immune parameters peaking at specific times of day [19]. Leukocytes extravasate from blood preferentially at the beginning of the behavioral active phase [20–22]. This rhythmic migration also occurs in cancer and results in a surprisingly dynamic circadian tumor immune microenvironment, where numbers of TILs peak at the onset of the active phase and trough during the rest phase [23,24]. Adoptively transferred leukocytes show similar trafficking patterns, driven by circadian rhythms in the microenvironment of the recipient and within the transferred cells themselves [21]. Specifically, blood endothelial cells (ECs) within the venous microvasculature gate leukocyte trafficking between blood and tissues via the circadian expression of adhesion molecules in both steady state and disease (Figure 1, Key figure) [21]. Depending on the tissue investigated, this has been shown for intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), P-selectin, and E-selectin, as well as other molecules (Table 1) [21,25]. Within the melanoma microvasculature, ICAM-1 expression peaks at the onset of the active phase, which has been associated with increased leukocyte infiltration into the tumor [23]. Deficiency of BMAL1 in ECs, and the subsequent lack of oscillations in this lineage, abolishes the rhythmic expression of ICAM-1 and consequently rhythmic migration. This demonstrates that the circadian clock in ECs acts as gatekeeper of the circadian infiltration of leukocytes to tumors [21]. Leukocytes themselves also express adhesion molecules in a circadian manner, such as L-selectin, $\alpha_L\beta_2$-integrin (LFA-1), and α_4-integrin (VLA-4) that control the circadian extravasation process [21]. Removal of the L-selectin receptor–ligand axis impairs the ability of T cells to migrate to lymph nodes and infiltrate melanomas [26]. In addition, blockade of LFA-1, the ICAM-1 ligand, renders infiltration of immune cells to tumors arrhythmic [23].

The rhythmic release of hormones and neurotransmitters further modulates leukocyte trafficking by controlling the expression of chemokines and their receptors. Glucocorticoids upregulate CXCR4 expression on leukocytes through the interleukin 7 (IL-7) receptor axis, promoting T cell homing to CXCL12-rich tissues [27,28]. In addition to glucocorticoids, the release of noradrenaline reduces CXCL9-dependent $CD8^+$ T cell infiltration into tumors [29]. T cells sense noradrenaline through β_2-adrenergic receptors, which enhances the functional responsiveness of CCR7 and CXCR4, promoting lymphoid tissue retention and reducing egress into efferent lymph and back into

Glossary

***BMAL1*:** a core circadian clock gene that forms a transcriptional activator complex with CLOCK to sustain the 24 h molecular feedback loop that drives circadian rhythms. *BMAL1* is unique as the only single clock gene whose absence abolishes circadian rhythmicity.
Chronotherapy: the administration of therapeutic treatments at a specific time or according to an individual's body rhythm. This approach leverages time-of-day-dependent variations in physiology to optimize treatment outcomes by maximizing efficacy and minimizing toxicity.
Circadian rhythms: endogenous ~24 h physiological and behavioral cycles orchestrated by the molecular circadian clock machinery. These rhythms persist even in the absence of external environmental cues such as light. However, these cues are required to synchronize an organism to the outside world.
Suprachiasmatic nucleus (SCN): the master circadian pacemaker located in the hypothalamus of the brain. The SCN coordinates circadian rhythms throughout the body by synchronizing cellular clocks to environmental signals, so that cells across the whole body work in line with each other.

Key figure

Circadian regulation of antitumor immunity in adoptive cell therapy

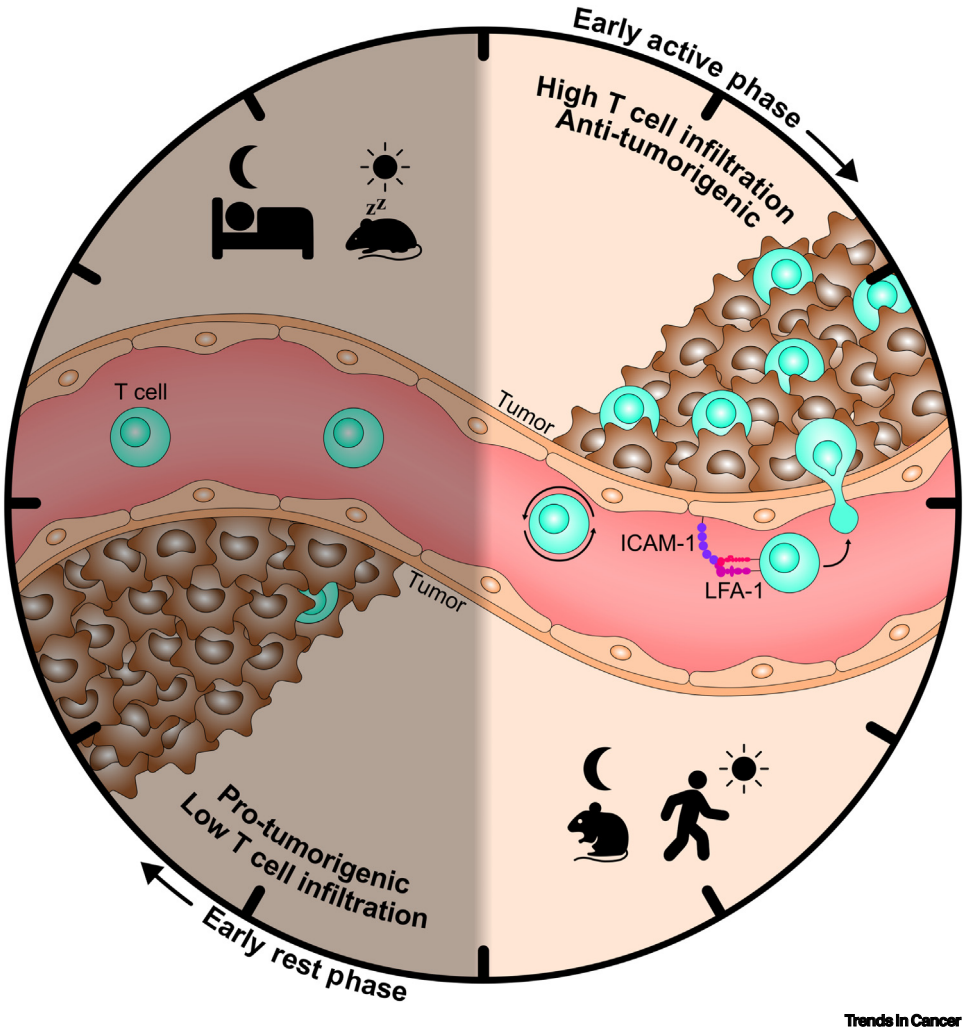

Figure 1. During the behavioral rest phase, the tumor microenvironment is less permissive to immune cell infiltration. By contrast, during the early behavioral active phase (corresponding to daytime in humans and nighttime in mice), adoptively transferred T cells show enhanced trafficking from the bloodstream into the tumor. This rhythmic migration is regulated by the circadian expression of endothelial adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), which interacts with $\alpha_L\beta_2$-integrin (LFA-1) on T cells. Upon tumor entry, T cells adopt either pro- or antitumorigenic phenotypes, influenced in part by the expression of exhaustion markers such as PD-1. The shaded area represents rest phases for both species.

blood [20,30]. Adrenergic stimulation before leukapheresis can mobilize a population of highly cytotoxic γδ T cells, potentially enhancing the quality and potency of ACT products when harvested during specific time windows [31]. Moreover, CAR-T cells engineered to express CXCR4 or CXCR5 exhibit improved tumor infiltration [32–34]. These data indicate that ToD-optimized ACT may benefit tumor immunotherapy by leveraging endogenous circadian cues that control tumor infiltration of leukocytes. Indeed, recent retrospectively analyzed clinical data of CAR-T cell therapy

Table 1. Key circadian-regulated migratory factors relevant for T cell tissue infiltration and function

Marker	Function	Peak time[a]	Fold change	Investigated species	Investigated cell	Investigated molecule	Binding partner	Refs
CCL21	Chemokine	ZT7–9	~3	Mouse	Lymphatic endothelial cells	Protein	CCR7	[20,50]
CCR7	Chemokine receptor	ZT13	~1.5	Mouse	T cells	Protein	CCL19, CCL21	[20,21]
CD99	Adhesion molecule	ZT19	~3	Mouse	Lymphatic endothelial cells	Protein	CD99	[50]
CXCR4	Chemokine receptor	ZT9	~2	Mouse	T cells	mRNA	CXCL12, CCL21	[20]
CXCR5	Chemokine receptor	ZT5	~1.2	Mouse	$CD8^+$ T cells	mRNA	CXCL13	[21]
E-selectin (CD62E)	Adhesion molecule	ZT13	~2	Mouse	Endothelial cells	mRNA	PSGL-1	[25]
ICAM-1	Adhesion molecule	ZT13	~2	Mouse	(Lymphatic) endothelial cells	Protein	LFA-1	[20,23,25]
JAM-A	Adhesion molecule	ZT7	~1.5	Mouse	Lymphatic endothelial cells	Protein	JAM-A	[50]
JAM-C	Adhesion molecule	ZT1	~1.5	Mouse	Lymphatic endothelial cells	Protein	Integrins	[50]
LFA-1 (CD11a)	Adhesion molecule	ZT21	~1.3	Mouse	T cells	Protein	ICAM-1, ICAM-2	[21]
L-selectin (CD62L)	Adhesion molecule	ZT17	~1.5	Mouse	T cells	Protein	GlyCAM-1, CD34	[21]
LYVE-1	Adhesion molecule	ZT1	~1.5	Mouse	Lymphatic endothelial cells	Protein	Hyaluronan	[50]
PD-1	Immune checkpoint receptor	42h after sync	~2	Human	*In vitro* synchronized T cells	mRNA	PD-L1, PD-L2	[23]
P-selectin	Adhesion molecule	ZT13	~1.3	Mouse	Bone-marrow endothelial cells	Protein	PSGL-1	[21,25]
PSGL-1	Adhesion molecule	ZT1	~1.2	Mouse	T cells	Protein	P-selectin, E-selectin	[21]
S1PR1	Lipid receptor (egress)	ZT7	~2	Mouse	T cells	Protein	Sphingosine-1-phosphate (S1P)	[20]
VCAM-1	Adhesion molecule	ZT13	~8	Mouse	Endothelial cells	Protein	VLA-4	[21,25]
VLA-4 (CD49d)	Adhesion molecule	ZT9	~1.5	Mouse	T cells	Protein	VCAM-1	[21]

[a]Zeitgeber time (ZT) refers to time after light onset within a 12 h:12 h light/dark schedule. *In vitro* cell cultures were synchronized (sync) for circadian expression analyses.

indicate improved overall survival in patients when CAR-T cells are infused at the onset or middle of the behavioral active phase (i.e., before 3 p.m.) [35]. In addition, preclinical evidence shows that both mouse TCR-engineered OT-I T cells in melanoma models and human CAR-T cells in a mouse xenogeneic lymphoma model exhibit enhanced tumor homing and decreased tumor growth when infused at the onset of the recipient's behavioral active phase [23]. Given the long half-life of these cells, however, it is astonishing that ToD of ACT exhibits such an effect. This is reminiscent of observations from preclinical data and retrospectively analyzed clinical trials of immune checkpoint inhibitors (ICIs) that show enhanced overall survival when ICIs are administered during the early behavioral active phase [36]. Future research will need to address the underlying

mechanisms for these ToD effects and why time of administration and the associated lack of efficacy at the wrong ToD cannot just simply catch up with the optimal time.

ToD shapes antitumor T cell phenotype

Beyond trafficking, T cell phenotype and function also oscillate with circadian rhythmicity, as shown in vaccination and tumor models [22,23]. During the behavioral rest phase, $CD4^+$ T cells express higher levels of metabolic enzymes related to lipid, ketone, and amine metabolism, resulting in lower proliferation capacity *in vitro* and *in vivo* [22]. Furthermore, activation-related genes, including IRF and BLIMP1, as well as TCR signaling pathways, involving ZAP70, AKT, and mTOR, are enriched during the late rest phase. These rhythmic differences are abolished in T cells lacking BMAL1, indicating a cell-autonomous role of the circadian clock in regulating T cell function [37]. Importantly, ZAP70, a key TCR signaling protein, is also central to CAR signaling via the CD3ζ domain [38], which may thus exert circadian effects on this therapy.

Within tumors, the phenotype of TILs is ToD-dependent, with increased antitumorigenic gene expression profiles observed during the early active phase [23]. The same T cell signatures that peak in mice during their active phase correlate with gene signatures in melanoma patients that are associated with improved survival, suggesting that circadian immune dynamics may be conserved across species and clinically relevant [23]. Importantly, one of the major limitations of ACT is the tendency of transferred T cells to enter a terminally exhausted state after sustained antigen exposure [39]. This exhaustion is characterized by the upregulation of inhibitory receptors such as PD-1 and CTLA-4. Notably, circadian clock gene expression has been shown to correlate with these exhaustion markers in the tumor microenvironment [40]. *In vitro, PDCD1* (encoding PD-1) exhibits circadian oscillation in activated human $CD8^+$ T cells, suggesting that transferred T cells may be more or less prone to exhaustion, depending on the ToD [23]. Furthermore, modulation of the circadian clock component RORγ with an agonist reduces PD-1 expression and improves tumor control in a preclinical ACT model [41]. These findings support the idea that transferred T cells are subject to ToD-dependent regulation of exhaustion and may adopt a more functional, antitumorigenic phenotype when administered at the onset of the active phase.

While no retrospective or prospective clinical trials have yet investigated the efficacy of ToD-optimized ACT infusion, the more antitumorigenic T cell phenotype at specific time windows points to a significant potential of ToD for enhancing ACT outcomes. Thus, circadian modulation of T cell metabolism, activation, and inhibition pathways, in addition to an enhanced capacity to infiltrate tumors, could affect CAR-T activity.

Reducing toxicity by circadian timing

ACTs can cause severe toxicities, including cytokine release syndrome (CRS) and neurotoxicity [15]. Timing ACT to a specific circadian window may therefore help mitigate these risks. For example, melatonin, a hormone produced by the pineal gland during the dark phase, reduces CRS severity in CAR-T models by dampening IL-6 and IL-1β production, without impairing antitumor activity [42]. In addition, pharmacological treatment with melatonin has been shown to downregulate LFA-1 expression on $CD8^+$ T cells, which may limit their tumor infiltration and promote retention in the bloodstream [43]. Melatonin levels are naturally low during the behavioral active phase in humans, when T cell tumor homing is predicted to be most efficient [23,44]. This suggests a potential trade-off between maximizing efficacy and minimizing toxicity when optimizing ToD in humans, highlighting the need to balance efficacy and safety when selecting the optimal ToD for infusion.

The high cost and logistical complexity of autologous ACT production limits accessibility, driving the need for off-the-shelf allogeneic cell therapies, which come at a minor risk of developing graft

versus host disease (GvHD) [45–47]. A recent paper indicates that acute GvHD (aGvHD), a life-threatening complication associated with allogenic hematopoietic stem transplantation (allo-HSCT), is highly ToD-dependent [48]. Reduced incidence of aGvHD was observed in two independent retrospectively analyzed cohorts of patients with hematological diseases when allo-HSCT was performed during the early active phase. Supporting preclinical data in mice revealed circadian variation in cytokine release and danger-associated molecular pattern (DAMP) signaling following total body irradiation as a conditioning regimen [48]. Conditioning the recipient during the active phase resulted in lower levels of IL-1α in the serum. IL-1α is a proinflammatory cytokine released during apoptosis that acts as a DAMP, contributing to immune activation [49]. As a result of reduced IL-1α secretion, T cells transferred during the early active phase exhibit diminished activation and differentiation into effector phenotypes, leading to a lower incidence of GvHD.

These findings underscore the potential of ToD-optimized interventions to mitigate adverse effects. Whether chemotherapy-based conditioning regimens commonly used in ACT protocols also exhibit ToD-dependent cytokine and DAMP release remains an open question warranting further investigation.

Concluding remarks and future perspectives

ACT has fundamentally reshaped the landscape of cancer treatment, but the potential impact of ToD optimization remains to be elucidated. Circadian rhythms shape T cell migration, activation, and phenotype, which are all critical to ACT success. Emerging evidence from both retrospective clinical data and preclinical models suggests that aligning ACT delivery with the early behavioral active time window of the recipient enhances efficacy and minimizes toxicity. However, prospective clinical trials have yet to demonstrate this in patients. Integrating ToD into clinical trial design may offer a low-cost, high-impact strategy to refine precision immunotherapy: **chronotherapy**. Thus, circadian-informed interventions, ranging from infusion timing to ToD-optimized conditioning, may unlock untapped potential for ACT. Several critical questions remain regarding the clinical application, underlying mechanisms, and optimization of ToD-based ACT protocols (see Outstanding questions), which will be key to address in the coming years.

Outstanding questions

Is time-of-day dependency in ACT efficacy observed in randomized clinical trials in different cancer types, including solid and hematologic tumors?

Why can T cells injected at suboptimal times not simply catch up to T cell injection at optimal times, given their long half-lives?

Are ToD effects due to differences in tumor infiltration and/or T cell behavior within the tumor?

Do commonly used lymphodepletion or conditioning regimens, such as chemotherapy or irradiation, exhibit ToD-dependent immune modulation that impacts ACT efficacy and safety?

Could pharmacological modulation of circadian regulators (e.g., BMAL1, REV-ERBs, RORs) improve ACT efficacy by phase shifting to optimal ToD and boosting circadian amplitude in patients with dampened rhythms?

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Declaration of interests

The authors declare no competing interests.

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