**Prof. Carrie Partch**
**Professor, Chemistry and Biochemistry Department, University of California, Santa Cruz USA**

UC SANTA CRUZ
**Chancellor Cynthia K. Larive**
chancellor@ucsc.edu

Our voices will define the century.
The real change is us.

January 23, 2024

Dear Selection Committee,

It is a profound honor to nominate my colleague Professor Carrie Partch for the Albert Einstein Science Award from the World Cultural Council. In my many years as an academic scientist, and now as chancellor, I have never before seen a young scientist rise to prominence so quickly and, while doing so, exhibit such scholarship and dedication to her field and to her students. Carrie is a phenomenal teacher and scientist, a world leader with excellent creativity, vision, judgment and values and, in my view, fully deserving of this high distinction. The accompanying reference letters detail Carrie's many accomplishments. With this letter, I will draw on my personal observations of Carrie as a scholar, mentor and teacher.

Carrie's research is on the structural biology of clock protein complexes that set the cellular timing for circadian rhythms. These protein complexes are emerging as critically important in a number of disease states linked to diabetes and cancer. Carrie's research is supported by a prestigious NIH MIRA grant, with a funding level roughly equivalent to two combined NIH grants. With publications in *Science, Nature, Nature Structural and Molecular Biology*, *Molecular Cell*, *Proceedings of the National Academy USA* and *Trends in Biochemical Sciences*, Carrie's work reveals the molecular underpinnings of how the cells in our body keep time. Just this year, Carrie published a full article in *Molecular Cell* reporting, for the first time, how the biochemical process of phosphorylation controls the circadian period (Mol Cell 2023 83:1677-1692). Her work has garnered attention in the national press (for example, Wired, Sept 26, 2015, Quanta Magazine, 2015) and numerous speaking invitations. Quanta Magazine completed a feature story on her career and remarkable research findings. Her work was also featured in many UC Santa Cruz press releases, for example the 2023 story "Study reveals key molecular interaction that sets the timing of our biological clocks." Additionally, a press release in 2020 caught the eye of the NIH Director, who then featured her work in his official blog.

In 2018, Carrie was awarded with Aschoff's Rule, the top award in the circadian rhythm field handed down annually between circadian biologists. That same year, she also received the Margaret Oakley Dayhoff Award, of the Biophysical Society, given to the nation's top early career, female researcher. Last year, Carrie was honored by the National Academy of Sciences with their annual award in Molecular Biology (https://news.ucsc.edu/2022/01/partch-nas-award.html) for her contributions to the molecular understanding of circadian rhythms. This is one of the most prestigious awards for a midcareer scientist, clearly marking Carrie as one of the standouts of her generation.

As Carrie's UC Santa Cruz colleague, I've had the wonderful opportunity to observe her interactions with students. Carrie is a remarkably selfless individual who is generous with her time and puts her all into teaching. Students in her classes are mesmerized by her enthusiasm, clarity and willingness to spend time with them. She sets high standards, and students respond by stepping up to grasp even the most complicated concepts. Passing by Carrie's office, it is common to see throngs of students camped out around her desk deeply engaged in discussions of macromolecular subtleties and biochemical control.

Consistent with Carrie's dedication in the classroom, she sensed a need to mentor students in the art of proposal writing. Of her own volition, Carrie developed a new graduate class with the goal of training students and postdoctoral researchers on how to write NSF and NIH fellowship applications. Throughout the course, students get first-hand writing experience, detailed critiques and, as expected, they absolutely love working with Carrie. The course, now offered annually, has caught fire and is in high demand from students across multiple science departments, including Biology, Bioinformatics, Microbiology, Chemistry and so forth. And the results have been amazing – many graduate and postdoctoral fellowships awarded to our trainees are a direct result of this remarkable class.

Carrie is also a major contributor to our campus's diversity, equity, inclusion and belonging efforts, expanding the opportunities available to underrepresented students. The proposal writing course described above has been instrumental in a multitude of successful diversity supplement applications to the NIH. As a testament to her sensitivity and dedication, Carrie worked with the Institute for the Biology of Stem Cells to conceive of the first Family Day that provided an exciting venue for families of underrepresented and first-generation students to experience the impact of what their sons and daughters, siblings and cousins are doing in research.

Carrie's dedication and enthusiasm are infectious, motivating her students to contribute beyond their laboratory research. Emulating Carrie, students dedicate themselves to advancing scientific discussion and outreach events for public benefit. For example, two of her graduate students helped launch the local Santa Cruz Chapter of Women in Sciences and Engineering (WISE) Science on Tap event, with invited monthly talks for the public at a local restaurant. These events are incredibly engaging and routinely sold out.

Professor Carrie Partch represents the very best one hopes to see in a world caliber scientist. Her science is outstanding, as evidenced by her top-flight publications, research funding and global influence. Along with her scientific success, she is selfless in teaching and public outreach and, importantly, sets the highest example for young scientists. Researchers at all scientific levels – undergraduate, graduate and postdoctoral – are deeply moved by Carrie's scholarship and dedication, and many are motivated to consider academic careers for themselves. I am pleased to offer my most enthusiastic recommendation for Carrie Partch and very much hope we can honor this exceptional scientist, teacher and scholar with the Albert Einstein Science Award from the World Cultural Council.

Sincerely,

Chancellor Cynthia K Larive

# Geisel School of Medicine at Dartmouth

**Jay C. Dunlap**
*Nathan Smith Professor*
*past Chairman, Department of Molecular and Systems Biology*

Hanover, New Hampshire 03755-3837
7400 Remsen Building

TEL. (603)650-1108
FAX (603)650-1233
Email: jay.c.dunlap@dartmouth.edu


Selection Committee
Albert Einstein" World Award of Science,
World Cultural Council,
Bulle, CH

January 21, 2024

Dear Members of the Selection Committee:

I write with my strongest support to nominate Carrie Partch, in the Department of Chemistry and Biochemistry at UC Santa Cruz, for the 2024 Albert Einstein World Award of Science. Dr. Partch's work has taken the circadian field to the next level of understanding by shedding light on the protein-based signaling mechanisms and structural assemblies that give rise to circadian rhythms.

I first became familiar with Dr. Partch a little more than a decade ago when she was a postdoc with Kevin Gardner at UT Southwestern. This was a time before structural approaches had provided much in the way of insights into clock proteins, but it was plain that she had the right tools, intellect, and drive to pioneer this journey. Speaking about this broadly though, Partch's niche proved to be optimal in some ways that were hard to predict at the time. Several labs in the field were attempting structural work, notably including Brian Crane at Cornell, but were attempting crystallizations rather than the NMR-based approaches championed by Partch. As it turned out, we and others found that salient clock proteins often worked through large intrinsically disordered regions regulated via extensive post-transcriptional modifications. This played perfectly to Partch's blended strengths in solution-based structure determination, crystallization, and now cryo-EM; these combined with her lightning-quick mind, cheerful personality that fosters collaborations, and take-no-prisoners approach to driving experiments, has allowed her in a short time to become the thought leader in circadian structural biology. I have followed her work closely, and drawn on her insights at meetings, but we have never published a paper together nor shared any past or planned funding. I have no conceivable conflict of interest to declare, and our mutual interests lie only in understanding the molecular bases of circadian rhythms writ large. From this point I'd like to lead you through the published record from this remarkable young scientist.

Partch's unique approach to the field, combining biochemistry, molecular biophysics, and structural biology began in her doctoral training with Aziz Sancar where she studied cryptochromes. These signaling proteins, first discovered by Tony Cashmore in plants, are structurally related to the DNA repair enzyme photolyase, but lack DNA repair activity. Her graduate work, early after the discovery of cryptochromes, provided the first molecular evidence for light-dependent conformational changes in *Arabidopsis* CRY1, a key protein that controls plant growth in response to blue light. Partch's *in vitro* work showed that light could initiate release of an autoinhibitory disordered tail from the FAD-binding photolyase homology region (PHR) to initiate the CRY signaling mechanism (Partch et al. (2005) *Biochemistry*). As you'll see below, she recently revisited this theme to highlight how a prevalent genetic variant leads to alterations in circadian rhythms and the timing of sleep onset in humans.

Partch worked as a postdoc with Kevin Gardner at UT Southwestern Medical Center, training in molecular biophysics and contributing insight into protein assemblies and transcriptional regulation by the basic helix-loop-helix and PAS domain-containing Hypoxia-Inducible Factor (HIF) (Partch, C. and Gardner, K. (2011) *PNAS*). Before taking her independent position at UCSC, she also worked with Joe Takahashi as part of the team that solved the first partial crystal structure of CLOCK:BMAL1, the bHLH-PAS transcription factor that controls mammalian rhythms, (Huang, N. et al. (2012) *Science*). In her own lab at UCSC since in 2011, Partch has developed a highly productive and impactful research effort that continues to reveal fundamental insights into the molecular basis of circadian rhythms.

Partch first returned to her roots to study the essential transcriptional repressors of the mammalian clock. In mammals CRYs are not photoresponsive but act as transcriptional repressors; Partch established the

molecular basis for how CRYs interact directly with CLOCK and BMAL1 to repress activity of the heterodimer and close the circadian feedback loop. Her lab was the first to show how CRYs bind to the transcriptional activation domain (TAD) of BMAL1 to compete directly with coactivators like CBP/p300, thus enabling direct repression of CLOCK:BMAL1 activity by sequestration of the TAD (Xu, H. et al. (2015) *Nat Struct Mol Biol*). Partch's training in NMR spectroscopy positioned the lab to discover an intrinsically slow conformational switch in the BMAL1 TAD that plays a critical role in establishing 24-hour timing (Gustafson, C. et al. (2017) *Mol Cell*). Consistent with this model, missense mutations perturbing this switch in BMAL1 elicit hours-long changes in the period of this transcription-based molecular clock; the elegance of the approach and this result were eye-openers for many in the field. Her lab also discovered a CLOCK paralog, PAS Domain-containing 1 (PASD1), that uses evolutionary conservation with CLOCK to bind to and inhibit CLOCK:BMAL1 when upregulated in human cancer (Michael, A. et al. (2015) *Mol Cell*). This showcases how the deep integration of biochemistry, biophysics and cell biology in Partch's lab has the potential to discover new mechanisms that govern the activation and repression of CLOCK:BMAL1 to control circadian rhythms.

Partch's lab went on to show that CRY proteins make stable complexes with CLOCK:BMAL1 by binding to both CLOCK *and* BMAL1. Although this bivalent interaction was suggested by genetic screens 15 years ago, it was Carrie's lab that unraveled the molecular basis for CLOCK binding, showing that the PAS-B domain of CLOCK docks into an evolutionarily conserved pocket in the PHR domain of CRY1 (Michael, A. et al. (2017) *PNAS*). This led directly to work on the protein dynamics at the secondary pocket of CRY1 and CRY2 that explained differences in their repressive functions in the molecular clock (Fribourgh, J. et al. (2020) *eLife*): CRY1 has a disordered serine-rich loop at the secondary pocket that confers a 20-fold higher affinity for CLOCK than the rigid loop found in CRY2, validating a decades' old observation that *Cry2*$^{-/-}$ mice have a long period clock because they are left with just the potent repressor CRY1, while *Cry1*$^{-/-}$ mice have short clocks with the weaker CRY2 repressor. Partch's group used x-ray crystallography and quantitative *in vitro* binding studies along with MD simulations from Florence Tama's group to show how interactions with the co-repressor PER2 remodel this loop on CRY2 to enhance its affinity for CLOCK:BMAL1. Altogether, these studies are the foundation of the current framework for understanding how interactions between clock protein components drive the assembly and activity of complexes that regulate the circadian transcriptional program in mammals.

Nobel Laureate Mike Young's lab reported a few years ago that a prevalent *CRY1* allele in humans, CRY1Δ11 which skips exon 11, leads to a lengthened circadian period and to the night owl-like behavior associated with Delayed Sleep Phase Disorder (Patke, A. et al. (2017) *Cell*). Their work suggested that CRY1Δ11 has an increased affinity for CLOCK:BMAL1 that enhances the transcriptionally repressed state of this complex. However, the deletion in CRY1Δ11 arises from altered splicing within the disordered tail of CRY1 and not in the PHR domain previously shown by Carrie's lab to interact directly with CLOCK and BMAL1, so it was unclear how this alteration to the CRY1 protein influenced CLOCK:BMAL1 activity. Coming full circle back to her graduate work with cryptochromes, Partch's lab discovered that the disordered tail of CRY1 also binds to its PHR domain to regulate affinity for CLOCK:BMAL1 (Parico, G. et al. (2020) *PNAS*). Incredibly, the short, 24-residue stretch encoded by exon 11 is necessary and sufficient to regulate binding of CLOCK into the secondary pocket of CRY1 PHR domain. These data provide a mechanistic basis for understanding how the dominant CRY1Δ11 allele has such powerful control over human behavior, and suggest a conserved mechanism through which cryptochromes from plants and insects to humans are regulated by their disordered tails.

The narrative to this point has been dominated by studies on cryptochromes, but Partch's work extends far beyond just these proteins. Using an innovative NMR-based kinase assay, Carrie's lab has worked with David Virshup to show how the dedicated clock kinase, Casein Kinase 1δ (CK1δ) is responsible for the slow, rate-limiting phosphorylation of a key regulatory site in the co-repressor PER2 associated with Familial Advanced Sleep Phase (FASP) Syndrome (Narasimamurthy, R. et al. (2018) *PNAS*). Her group then discovered that CK1δ uses an anion-driven conformational change in its unique activation loop to regulate substrate selectivity on PER2 and control clock timing (Philpott, J. et al. (2020) *eLife*). This study made a fundamental connection between kinase mutants isolated from *Drosophila*, hamster, mouse and humans that link dynamics on the kinase to PER degradation, establishing a kinase 'code' for clock regulation that was featured in the NIH Director's Blog last February. Put simply, Partch's work

has provided fundamental mechanistic insights into the molecular basis of circadian rhythms in animals, knowledge that has provided profound insights into activities as basic to human biology as sleep.

All this might alone be enough to justify an award as salient as the Einstein World Award of Science, but Partch's contributions to rhythms also reach beyond animal clocks. In 2017, she collaborated with Andy LiWang and Susan Golden to unravel the structural basis for the cyanobacterial circadian clock. The mechanism of this remarkable oscillator is wholly distinct from the transcription/translation feedback loops of animals and fungi – this clock can run *in vitro* with just three purified proteins (KaiA, B and C) using $Mg^{2+}$ and ATP as an energy source. KaiC, the central enzymatic driver of this oscillator, sequentially autophosphorylates just two sites during the day under stimulation by KaiA, and sequentially dephosphorylates them at night when KaiB somehow inhibits KaiA. Partch's lab solved crystal structures to reveal how KaiB binds KaiC and sequesters KaiA at night, revealing a remarkable, transient, fold-switched structure of KaiB, one never seen before, that is stabilized by KaiC and holds it in an autoinhibited conformation (Tseng, R. et al. (2017) *Science*). This landmark study revealed truly astonishing new molecular details about this circadian clock, providing a quantal leap in understanding.

One of the additional surprising details from Tseng et al. has recently led to a structural understanding of how the cyanobacterial clock responds to light/dark cycles. CikA, an output kinase/phosphatase that communicates temporal information from the oscillator to the cell, also competes with KaiA for the same binding site on KaiB-KaiC. Oxidized quinone levels that naturally rise in the dark are bound by CikA, reducing its affinity for KaiC, allowing KaiA to bind, in this way entraining the clock to the external environment. In their efforts to address this new insight, Partch's partnership with LiWang and Golden yet again struck gold—they developed an extremely clever fluorescence anisotropy-based assay for monitoring *in vitro* rhythms that allowed them, for the first time, to reconstitute an intact circadian clock system *in vitro* containing input, oscillator and output proteins, all the way down to visualizing rhythmic binding of the circadian response regulator RpaA to its cognate promoter (Chavan, Swan, Heisler et al. *Science* 2021; Chavan et al. 2020). Using this new assay, Partch's lab probed the mechanistic basis for cooperative recruitment of 6 KaiB monomers to the KaiC hexamer, discovering that structural mimicry between the active conformation of KaiB and the thioredoxin-like domain in the output protein SasA is essential for maintaining robustness of the clock to changing concentrations of KaiB *in vivo* (Chavan, Swan, Heisler et al. *Science* 2021; Heisler, Swan et al. 2020).

Finally, (Swan, Sandate et al. 2021), Partch's lab, in collaboration, has answered one of the last fundamental questions about the mechanism of the cyanobacterial clock: How does the cycle of phosphorylation on the C-terminal ATPase domain of KaiC restrict, to the evening, association of clock proteins 70 angstroms away on its N-terminal domain? She worked with Gabe Lander's group to address this, solving cryo-EM structures of daytime and nighttime phosphomimetics to show how specific phosphorylation states influence the structural dynamics of KaiC. This allowed her to trace an allosteric pathway through KaiC that reveals how intersubunit interactions in the KaiC hexamer set the stage for the cooperative recruitment of KaiB. Here as before, her ability to identify the most pressing mechanistic questions and address them with rigorous experiments is remarkable.

Altogether, Partch has made numerous outstanding contributions to the field of circadian rhythms. Her work was recognized early on with the SRBR Junior Faculty Research Award (one awardee every two years), and later the 2018 Margaret Oakley Dayhoff Award from the Biophysical Society, the Aschoff's Rule, one of the top honors in our field that is handed down annually, and of note, the 2022 US National Academy of Sciences Award in Molecular Biology. Her passion for protein science and her visceral appreciation for the deep insights that biophysics and biochemistry can bring to probe the mechanistic basis of circadian rhythms warrants her receipt of the Albert Einstein World Award of Science.

Sincerely,

Jay C. Dunlap
Member, NAS

MRC Laboratory of Molecular Biology

Michael Hastings, PhD, FMedSci., FRS
Programme Leader, Neurobiology Division

Tel: (direct) +44 (0)1223 267045
Fax: (direct) +44 (0)1223 268305
Email: mha@mrc-lmb.cam.ac.uk

22nd January 2024

To the Selection Committee,
"Albert Einstein" World Award of Science,
World Cultural Council,
Bulle, CH.

Dear Selection Committee,

**Letter of support for the nomination of Dr. Carrie Partch, UC Santa Cruz**

I am thoroughly delighted to be able to write this letter of unequivocal support for Dr. Carrie Partch in her nomination for the "Albert Einstein" World Award of Science. I am familiar with her work via the literature and scientific meetings because of our common interest in circadian biology. I have published two papers with her as co-authors but not senior authors, and otherwise I have no conflict of interest to declare.

In both a personal and a professional capacity, I hold Carrie in the highest possible regard: as scientist, colleague and mentor to others. She has made world-leading contributions to circadian biology, in which she is an established star. Circadian body clocks are the cellular mechanisms that drive our daily rhythms of physiology and behaviour, the most obvious rhythm being the cycle of sleep and wakefulness. Under-pinning this, however, are cycles of brain and cellular activity and metabolism such that all of our internal processes are co-ordinated on a 24 hours basis. Moreover, these are true clocks insofar as they continue to keep approximately daily time autonomously, in the absence of external cues: down a cave, during a space orbit or in an experimental research facility. When our circadian system is disrupted, for example with shift work, night-time exposure to light, or in ageing and dementia, it carries a major burden on our health. Furthermore, such difficulties are increasingly prevalent in modern society.

Carrie has brought unrivalled insight into how our cells can define ~24 hours time. She achieved this by bringing her skills and insights in structural and molecular biology, alongside biophysical analysis, to the examination of circadian timing mechanisms. Moreover, she has done so at taxonomic scale, making seminal discoveries from single-celled cyanobacteria to humans. Her portfolio of research is truly outstanding, and I fully endorse the nomination.

Below, I list in detail some of Carrie's principal scientific achievements, but before that I wish to make a general point. The genetic decoding of circadian clockworks has been a standout success for the "clocks" field. We now speak of "mechanisms" with conviction, and we now understand the fundamental importance of circadian time-keeping to life on Earth: its prevalence within individual organisms and its ubiquity between taxa. As a consequence, we have a clear view on its relevance to health and disease. Nevertheless, we should not lose sight of the fact that the job is barely started. Deciphering circadian biology in all of its manifestations is a "big problem" and the genes are only the entry point. To understand how circadian mechanisms work, we need to decipher how the encoded proteins operate and thereby control cellular function in time. This is why I so admire Carrie's work, because she has brought the power and elegance of structural biology and biophysics to circadian biology. In doing so, she has opened out a new and critically necessary level of analysis of the properties and behaviours of "clock proteins" inside our daily timer. Furthermore, she has accomplished this employing diverse

model organisms (in her case, mammals and cyanobacteria) and seeking to enhance the wider translation of the clock (in her case, sleep and cancer). My second motivation arises from my experience of how she operates on a personal level. She is hugely collegial, open to new ideas and opportunities and relentlessly supportive and positive about her work and about the work of others. She already enjoys all of the hallmarks of a leader and is a considerable force in clock (and other) biology.

***Detailed scientific contributions.***

The clocks of eukaryotes assemble around transcriptional/ post-translational negative feedback loops (TTFLs) in which positive activators drive the expression of negative regulators, leading to a ~24 hours periodic cycle of gene expression and suppression, interlinked with cyclical protein synthesis and degradation. Genetic analyses, originally from the DNA repair field, identified cryptochrome (CRY) proteins as negative regulators, but how do these derivatives of photolyase enzymes work within the timer? In a series of landmark papers, Carrie has provided detailed mechanistic insight into how they interact directly with the positive activators, CLOCK and BMAL1 to repress their activity at the *Cry* (and *Period*) genes, thereby closing the feedback loop of the molecular circadian clock. Working at times with an admirable selection of collaborators, she identified how CRYs bind directly to the BMAL1 trans-activation domain to compete with the co-activators CBP and p300 to create the negative feedback about which the entire mammalian clock pivots. Expanding on this, she has revealed the structural basis of interactions between CRY and CLOCK PAS-B and how a slow conformational switch in the BMAL1 trans-activation domain contributes to setting the pace of the clock. This was especially exciting because a central but unresolved question in clock biology was how does it operate with such a long time-base, when protein interactions, as with so much else in biochemistry and intracellular biology, are pretty rapid. Here, Carrie discovered an intra-molecular timing mechanism that contributes to the circadian time-course of ~24 hours. She went on to reveal the molecular mechanisms underlying the differential contributions of CRY1 and CRY2 within the TTFL, and most recently discovered how Exon 11 in the CRY1 tail acts as an auto-inhibitory motif to control CRY1 association with CLOCK:BMAL1. This immediately provided a mechanistic explanation for the independently discovered familial delayed sleep syndrome in humans that carry the *Cry1Δ11* allele: a remarkable synthetic coming together of basic structural biology and human health.

Human familial circadian sleep disturbances can also be linked to mutations in the second group of negative regulators, the PER proteins and the kinases, CK1δ and CK1ε, that act on them. The mechanisms behind the phenotypes were, however, unknown: but Carrie has now discovered the causal molecular events that control the activity and stability of PER2, and thereby exert a powerful effect on human circadian timing and sleep. Working with David Virshup, a pioneer in the genetic analyses, she showed that CK1δ and CK1ε prime phosphorylation of the Familial Advanced Sleep Phase (FASP) region of PER2 in a rate-limiting step that triggers a downstream cascade of clock-relevant changes. She then discovered a two-state molecular switch in the CK1 kinase activation loop that directly regulates substrate specificity on either the Degron or the FASP region of PER2. With great elegance and molecular detail, this observation was able to explain the various and long-known short period phenotypes observed in *Drosophila*, rodents and humans.

Carrie's insights and discoveries are not limited, however, to animals, and working with a different team of collaborators, she has determined the structural basis of the cyanobacterial circadian clock. Other than the incorporation of a delayed negative feedback motif, this system is completely orthogonal to the TTFL of eukaryotes, not least because the definition of circadian time revolves around a series of intra- and inter-molecular reactions involving an assembly of just three proteins, the KaiA, B and C complex. Prior studies had shown that circadian cycles of phosphorylation states within the complex arise spontaneously: the clock is a self-sustaining post-translational oscillator, requiring only ATP to proceed. Meticulous understanding of the detail of molecular conformations and their progressive, slow transformations mediated by local catalytic events has been the defining key to Carrie's success in this field. First, she used X-ray crystallography to determine how the Kai proteins assemble into a large hexameric complex, defining the basis of the night-time repressive state that inhibits down-stream gene expression as a clock output. From this, she showed how protein interactions drive the post-translational

oscillation. The next challenge was to probe, in depth, the role of other proteins in governing the input and outputs from the KaiABC clockwork. How does it relate to the cell, because a clock with no connections to the cell is without biological value? By developing a novel high-throughput assay to reconstitute an intact molecular clock, Carrie and colleagues elucidated the contribution of kinase activity from output proteins CikA and SasA to control circadian programmes of downstream gene expression that ultimately coordinate cellular activity. She also defined the role of structural mimicry in the active conformation of KaiB and in a domain in SasA to regulate co-operative recruitment and assembly of robustly circadian complexes. Most recently, she has used electron cryomicroscopy to solve several structures of daytime and night-time complexes to reveal how changes in KaiC phosphorylation temporally restrict clock protein association to the evening. She has dissected the cyanobacterial clock into its molecular parts and then shown how they interact to keep time.

To conclude, even though the molecular architectures of cyanobacterial and mammalian clocks are totally different, Carrie has provided unprecedented insights into both systems, delivering the full story from atomic detail to in vivo biological function. By all markers of academic esteem, she is outstanding and in a position of global leadership. I note with pleasure the achievements of former recipients of the “Albert Einstein” World Award of Science and I am unswerving in my view that Carrie Partch is able to match them. I believe that she is eminently suitable for recognition by the World Cultural Council: doing so will not only recognise her achievements, but it will also provide a role model to many others.

I whole-heartedly encourage you to do so.

Yours sincerely,

Michael H. Hastings, PhD, FMedSci., FRS

Programme Leader,
Past Head of Neurobiology Division,
Neurobiology Division,
MRC Laboratory of Molecular Biology,
Cambridge U.K.

Carrie's work has showcased the importance of structural biology, biophysics, and biochemistry in revealing mechanisms of the molecular circadian clock that aligns our physiology and behavior with the solar day on Earth. Her work has taken the field to the next level by shedding light on the protein-based signaling mechanisms and structural assemblies that give rise to circadian rhythms within our cells to control how we interface with the world.

Carrie's unique approach to the field began in her doctoral training with Aziz Sancar, where she first studied the structure and function of cryptochromes. These signaling proteins are structurally related to the DNA repair enzyme photolyase but lack DNA repair activity. Her work provided the first biochemical evidence for light-dependent conformational changes in *Arabidopsis thaliana* CRY1, a protein that controls plant growth in response to blue light. Carrie showed that light could initiate release of an autoinhibitory disordered tail from the FAD-binding photolyase homology region (PHR) in plant CRYs to initiate signaling, and that these disordered tails are conserved in mammalian cryptochromes (Partch, C. et al. (2005) *Biochemistry*). In her postdoctoral work, she worked with Joe Takahashi as part of the team that solved the first crystal structure of the bHLH-PAS transcription factor that controls circadian rhythms, CLOCK:BMAL1 (Huang, N. et al. (2012) *Science*). Since beginning at UCSC in 2011, Carrie has developed a highly productive and impactful research group that continues to reveal fundamental insights into the molecular basis of circadian rhythms.

Carrie returned to her roots to discover how cryptochromes fulfill their roles as essential transcriptional repressors in the mammalian circadian clock. Her lab was the first to show how CRYs bind to the transcriptional activation domain (TAD) of BMAL1 to compete with coactivators like CBP/p300, thus enabling direct repression of CLOCK:BMAL1 activity by sequestration of the TAD (Xu, H. et al. (2015) *Nat Struct Mol Biol*). Her lab discovered an intrinsically slow conformational switch in the BMAL1 TAD that plays a critical role in establishing 24-hour timing (Gustafson, C. et al. (2017) *Mol Cell*). Clock reconstitution studies of *Bmal1*$^{-/-}$ cells with point mutants locking this switch in BMAL1 elicit hours-long changes in the period of the transcription-based molecular clock, and she recently showed how interactions with nucleosomes facilitate the Pioneer activity of this essential circadian transcription factor (Michael, A. Et al. (2023) *Nature*). Carrie's lab also discovered a CLOCK paralog, the cancer/testis antigen PAS Domain-containing 1 (PASD1), that uses evolutionary conservation with CLOCK to inhibit CLOCK:BMAL1 when it is upregulated in human cancer (Michael, A. et al. (2015) *Mol Cell*). This showcases how the deep integration of biochemistry, biophysics and cell biology in Carrie's lab has the potential to discover new mechanisms that govern the activation and repression of CLOCK:BMAL1 to control circadian rhythms.

Carrie's lab went on to show that CRY proteins make stable complexes with CLOCK:BMAL1 by binding to both CLOCK *and* BMAL1, showing that the PAS-B domain of CLOCK docks into an evolutionarily conserved pocket in the PHR domain of CRY1 (Michael, A. et al. (2017) *PNAS*). They then showed that protein dynamics at the secondary pocket of CRY1 and CRY2 account for their different repressive functions in the molecular clock (Fribourgh, J. et al. (2020) *eLife*). CRY1 has a disordered serine-rich loop at the secondary pocket that confers a 20-fold higher affinity for CLOCK than the rigid loop found in CRY2, validating a decades' old observation that *Cry2*$^{-/-}$ mice have a long clock because they are left with just the potent repressor CRY1, while *Cry1*$^{-/-}$ mice have short clocks with weaker CRY2 repressor. Carrie's group then showed how interactions with the co-repressor PER2 remodel this loop on CRY2 to enhance its affinity for CLOCK:BMAL1, providing a framework to understand how interactions between clock proteins play a role in the assembly and activity of complexes that regulate the circadian transcriptional program in mammals.

Mike Young's lab at Rockefeller discovered a prevalent human allele in *Cry1* that leads to a lengthened circadian period and the extreme night owl-like behavior associated with Familial Delayed Sleep Phase Disorder (Patke, A. et al. (2017) *Cell*). That work suggested that the CRY1Δ11 allele has an increase in affinity for CLOCK:BMAL1 to enhance the transcriptionally repressive state. However, the deletion of exon 11 in this allele arises from altered splicing within the disordered tail of CRY1 and not the PHR domain that was shown to interact directly with CLOCK and BMAL1 by Carrie's lab. Coming full circle, Carrie's lab discovered that the disordered tail of CRY1 binds to its PHR domain to regulate its affinity for CLOCK:BMAL1 (Parico, G.C. et al. (2020) *PNAS*). Incredibly, the short, 24-residue stretch encoded by exon 11 is necessary and sufficient to regulate binding of CLOCK into the secondary pocket of CRY1 PHR domain. These data provide a mechanistic basis to understand how this dominant allele has such powerful control over human behavior and suggest a conserved mechanism by which cryptochromes from plants and insects to humans are regulated by their disordered tails.

Carrie's work in the animal circadian clock has not been limited to cryptochromes. Using an innovative NMR-based kinase assay, Carrie's lab showed that the dedicated clock kinase Casein Kinase 1δ (CK1δ) is responsible for the slow, rate-limiting phosphorylation of a key regulatory site in the co-repressor PER2 associated with Familial Advanced Sleep Phase (FASP) in humans (Narasimamurthy, R. et al. (2018) *PNAS*). Her group showed that this poorly characterized kinase uses an anion-driven conformational change in its activation loop to regulate substrate selectivity on PER2 and control clock timing (Philpott, J. et al. (2020) *eLife*). These studies were then extended to identify the molecular basis by which mutations in this critical regulatory region in PER2 lead to dramatic (~4-hr) changes in circadian period and sleep phase syndromes in humans (Toh et al. (2001) *Science*). Her lab discovered that phosphorylation of a multi-serine cluster in the so-called FASP region of PER2 by CK1δ generates a product-based inhibitor that binds to conserved anion binding sites on the kinase *to* keep it in an inactive state while bound to adjacent anchoring domains (Philpott et al. (2023) *Mol Cell*). Remarkably, this mechanism of feedback inhibition is functionally conserved in the *Drosophila* clock; Carrie's lab showed that the *per-short* mutation first identified by Konopka and Benzer in 1971 (*PNAS*) eliminates a CK1-dependent phosphorylation site near the conserved kinase binding domain that serves the same purpose to inactivate the stably bound kinase. This regulatory site on the kinase is conserved to near histone-like levels (>95% identity) throughout eukaryotes, where CK1 has been implicated in the control of circadian timing, providing insight on how this kinase interacts with and regulates a genetically diverse of eukaryotic clock protein effectors.

Carrie's contributions to circadian rhythms extend beyond eukaryotic clocks. In 2017, her lab determined the structural basis for assembly of Kai protein complexes in the cyanobacterial circadian clock in collaboration with Andy LiWang. This remarkable circadian clock can keep time *in vitro* with just three purified proteins (KaiA, B and C) using $Mg^{2+}$·ATP as an energy source. Leveraging a version of KaiB 'locked' into an active conformation, Carrie's lab solved several crystal structures to reveal how KaiB binds to KaiC to sequester KaiA at night and maintain it in an autoinhibited conformation (Tseng, R. et al. (2017) *Science*). This landmark study revealed many molecular details about this circadian clock that had been missing despite the tractability of studying this *in vitro* clock.

Together, Carrie and Andy used this structural information to develop an innovative fluorescence polarization-based assay to monitor the oscillator in high-throughput in a non-invasive way *in vitro*. Using these assays, their labs developed a protocol to site-specifically label each of the oscillator components as well as input and output factors, allowing them to reconstitute a full *in vitro* clock that reads out rhythmic binding of the canonical response regulator to its cognate DNA in response to temporal cues (Chavan, A. et al. (2021) *Science*). This new assay also allowed them to dissect the roles of input and output factors, leading to the surprising discovery that structural mimicry of the active confirmation of KaiB by the output histidine kinase SasA allows it to cooperatively recruit KaiB and enhance robustness of the clock *in vivo*, where Susan Golden's lab showing that mutations the uncouple KaiB recruitment from its histidine kinase activity functionally mimic the SasA knockout in *S. elongatus*.

Carrie's lab also tackled one of the last fundamental questions about the molecular basis of cyanobacterial circadian rhythms—how day/night information gets communicated from one end of KaiC to the other to temporally control its association with KaiB. KaiC preferentially phosphorylates itself during the day with the help of KaiA, while it autodephosphorylates at night to create a ~24-hour rhythm in its phosphorylation. Numerous crystal structures of KaiC phosphoforms that represent the daytime or nighttime state published more than a decade ago all had the same structure, so it was unclear how phosphorylation 'communicates' day/night information through KaiC to selectively restrict KaiB binding to nighttime. Their cryo-EM studies revealed a dramatic change in conformation of KaiC between its daytime and nighttime states, with quantitative mutagenesis studies probing the allosteric pathway to show how phosphorylation regulates cooperative binding of KaiB monomers over ~80 Å away (Swan, J. et al. (2022) *Nat Struct Mol Biol*).

Our lives are intimately linked to the day/night cycle, with biological clocks that tick in each of our cells. Carrie's lab has made a number of outstanding contributions to the field of circadian rhythms by bringing quantitative and mechanistic studies to proteins of circadian clocks. These contributions benefit mankind by helping us better understand how these clocks work and serving as a platform for therapeutic strategies that will allow us lead healthier lives here on Earth and beyond.

**Carrie L. Partch**
**Curriculum vitae**

1156 High St.
Dept. of Chemistry and Biochemistry
University of California Santa Cruz
Santa Cruz, CA 95064
Phone: (831) 459-3905
cpartch@ucsc.edu

## Vision

Our lab works to identify the structural and biochemical underpinnings of biological timekeeping by circadian clocks, which synchronize physiology and behavior with the day/night cycle. By developing a mechanistic understanding of how molecular circadian clocks function, we aim to capitalize on the temporal regulation of physiology and behavior to develop innovative strategies to treat a broad spectrum of human diseases.

## Positions and Employment

| | |
|---|---|
| 2019 – | Professor, Chemistry and Biochemistry Department, UC Santa Cruz |
| 2017 – 2019 | Associate Professor, Chemistry and Biochemistry Department, UC Santa Cruz |
| 2011 – 2017 | Assistant Professor, Chemistry and Biochemistry Department, UC Santa Cruz |
| 2010 – 2011 | Postdoc research with Dr. Joseph Takahashi, Howard Hughes Medical Institute and University of Texas Southwestern Medical Center |
| 2006 – 2010 | Postdoc research with Dr. Kevin Gardner, University of Texas Southwestern Medical Center |
| 2000 – 2006 | Graduate research with Nobel Laureate Dr. Aziz Sancar, University of North Carolina Chapel Hill; Ph.D. thesis: “Signal transduction mechanisms of cryptochrome” |
| 1997 – 2000 | Research Technician with Dr. Daniel Carr, Oregon Health Sciences University |

## Education

| | |
|---|---|
| 2000 – 2006 | Ph.D., Biochemistry and Biophysics, University of North Carolina Chapel Hill |
| 1992 – 1997 | B.S., Biochemistry with minor in Italian, University of Washington |

## Honors, Fellowships and Awards

| | |
|---|---|
| 2022 | US National Academy of Sciences Award in Molecular Biology |
| 2018, 2019 | Finalist, UCSC Excellence in Teaching Award |
| 2018 | Aschoff’s Rule, a top award in the field handed down annually between circadian biologists |
| 2018 | Margaret Oakley Dayhoff Award, Biophysical Society |
| 2016 | Junior Faculty Research Award, Society for Research on Biological Rhythms |
| 2010 | Dean’s Award for Excellence in Postdoctoral Research, UTSW Graduate Division |
| 2008 – 2010 | Postdoctoral National Research Service Award, National Cancer Institute |
| 2007 | Chilton–Bell Fellowship, A.L. Chilton Foundation and Dept. of Biochemistry, UTSW |
| 2007, 2008 | Sigma Xi Award, University of Texas Southwestern Postdoctoral Association Symposium |
| 2003 – 2006 | Predoctoral National Research Service Award, National Institute of Mental Health |
| 2005 | Lineberger Graduate Fellow in Basic Sciences (highest thesis honor), UNC |
| 2000 | Irvin R. Logan Fellowship, Dept. of Biochemistry and Biophysics, UNC |

## Selected Invited Seminars and Presentations since 2018:

| | |
|---|---|
| 2024 | Gordon Research Conference on Intrinsically Disordered Proteins (Switzerland) |
| 2023 | Keynote address, Bay Area Chemistry Symposium (UCSF) |
| 2022 | Stanford University, Frontiers in Biology series student invitee |
| 2021 | Vanderbilt University, Dept. of Biochemistry |
| 2020 | Keynote address, Chilean Society for Biochemistry and Molecular Biology |
| 2019 | Gordon Research Conference on Chronobiology (Barcelona, Spain) |
| 2018 | Timelines in Biology Symposium, Weizmann Institute of Science (Rehovot, Israel) |
| 2018 | MRC Laboratory of Molecular Biology Seminar, Neurobiology/Cell Biology Groups (Cambridge, UK) |
| 2018 | Salk Institute / Ipsen Foundation / Science Magazine Symposium on Biological Complexity, “Biology of Time” (La Jolla, CA) |

**Selected Research Publications since 2018:**

Michael, A.K.*, Stoos, L.*, Crosby, P., Eggers, N., Nie, X.Y., Makasheva, K., Minnich, M., Healy, K.L., Weiss, J., Kempf, G., Cavadini, S., Kater, L., Seebacher, J., Vecchia, L., Chakraborty, D., Isbel, L., Grand, R.S., Andersch, F., Fribourgh, J.L., Schübeler, D., Zuber, J., Liu, A.C., Becker, P.B., Fierz, B., Partch, C.L., Menet, J.S., Thomä, N.H. (2023) Cooperation between bHLH transcription factors and histones for DNA access. *Nature*, 619: 385-393

- Featured in Murawska, M. et al. (2023) Pioneers conquer core histones at the chromatin frontier. *Nat Struct Mol Biol*, 30: 1050-1053

Philpott, J.M., Freeberg, A.M., Park, J., Lee, K., Ricci, C.G., Hunt, S.R., Narasimamurthy, R., Segal, D.H., Robles, R., Cai, Y.D., Tripathi, S., McCammon, J.A., Virshup, D.M., Chiu, J.C., Lee, C.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2023) PERIOD phosphorylation leads to feedback inhibition of CK1 activity to control circadian period. *Mol Cell*, 83: 1677-1692

Swan, J.A.*, Sandate, C.R.*, Chavan, A., Freeberg, A.M., Etwaru, D., Ernst, D.C., Palacios, J.G., Golden, S.S., LiWang, A., Lander, G.C.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2022) Coupling of distant ATPase domains in the circadian clock protein KaiC. *Nat Struct Mol Biol* 29: 759-766

Chavan, A.*, Swan, J.A.*, Heisler, J.*, Sancar, C., Ernst, D.C., Fang, M., Palacios, J.G., Spangler, R.K., Bagshaw, C.R., Tripathi, S., Crosby, P., Golden, S.S., Partch, C.L.$^{\Delta}$, LiWang, A.$^{\Delta}$ (2021) Reconstitution of an intact clock reveals mechanisms of circadian timekeeping. *Science* 374(6564): eabd4453

- Featured in Rust, M.J. (2021) Biological rhythms: The suspended animation clock. *Curr Biol* 31: R1513-R1534

Parico, G.C.G., Perez, I., Fribourgh, J.L., Hernandez, B.N., Lee, H.-W., Partch, C.L. (2020) The CRY1 tail controls circadian timing by regulating its association with CLOCK:BMAL1. *Proc Natl Acad Sci USA* 117: 27971-27979

Fribourgh, J.L.*, Srivastava, A.*, Sandate, C.R.*, Michael, A.K., Hsu, P.L., Rakers, C., Nguyen, L.T., Torgrimson, M., Parico, G.C., Tripathi, S., Zheng, N., Lander, G.C., Hirota, T., Tama, F.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2020) Dynamics at the serine loop underlie differential affinity of cryptochromes for CLOCK:BMAL1 to control circadian timing. *eLife*, doi: 10.7554/eLife.55275

Philpott, J.M.*, Narasimamurthy, R.*, Ricci, C.G.*, Freeberg, A.M., Hunt, S.R., Yee, L., Pelofsky, R.S., Tripathi, S., Virshup, D.M.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2020) Casein kinase 1 dynamics underlie substrate selectivity and the PER2 circadian phosphoswitch. *eLife*, doi: 10.7554/eLife.52343

- Featured in NIH Director's Blog "Early riser or night owl? New study may help to explain the difference" (Feb. 25, 2020)

**Molecular Animations**

Swan, J., Lopez-Rivera, F., Iwasa, J., Partch, C.L. (2023) KaiC and the cyanobacterial circadian clock. https://vimeo.com/789040719

**Teaching**

BIOC 100B: Advanced Biochemistry: undergraduate course in protein biochemistry covering ligand binding and allostery, enzyme kinetics and regulation, principles of intracellular signaling, and transport through membranes. (Winter Quarter 2014 – 2020)

CHEM 230: Grant Writing: graduate course on grant writing that focuses on principles of science writing and data presentation. Students write and peer edit written materials for the NIH Ruth L. Kirschstein F31 fellowship in the 10-week course. (Spring Quarter 2013 – 2022)

**Selected Talks and Outreach Activities since 2018:**

2016–2022 "Circadian rhythms: a look at how the clock controls your physiology", UCSC COSMOS (California State Summer School for Mathematics and Science) Discovery lecture series
2016-2021 Protein Crystallography Workshop, MARC (Maximizing Access to Research Careers) Summer Research Institute; week-long lecture and hands-on lab focused on x-ray crystallography for underrepresented STEM undergraduates at UCSC
2019 UCSC Emeriti Faculty Group and Women's Club, "Morning larks and night owls: how circadian timing influences your life"
2018 UCSC Original Thinkers series: "Earth Night: The human and environmental costs of artificial light at night"
2018 "Mentoring–how to give it and how to get it" Session Co-Chair, UC Presidential Postdoctoral Fellowship Annual Meeting

**Professional and Other Activities**

Memberships

2015 – Member, Biophysical Society
2014 – Member, The Protein Society
2013 – Member, American Society for Biochemistry and Molecular Biology
2011 – Affiliate member, UC San Diego Center for Circadian Biology
2011 – Member, Society for Research on Biological Rhythms (SRBR)
2011 – Member, American Chemical Society

Society works and conference organizing

2023 – Co-organizer, EMBO Biological Oscillators meeting (EMBL, Heidelberg, Germany)
2022 – Co-organizer, First International Meeting on Casein Kinases, Pasteur Institute (Paris, France)
2021–2023 Program Committee and Fundraising Chair, 2023 GRC Chronobiology meeting
2020–2023 Executive Council member, The Protein Society
2020–2022 Secretary, Board of Directors, SRBR
2019 Co-organizer, 2019 Bay Area Sleep and Circadian Research Meeting, NASA Ames
2018 – 2019 Co-organizer, 2019 West Coast Structural Biology Workshop (WCSBW), Asilomar
2018 Co-organizer, UCSC Original Thinkers event "Earth Night: The human and environmental costs of artificial light at night"
2018 – 2020 Member-at-large, Board of Directors, SRBR
2018 – 2021 Member, Public Affairs Committee, Biophysical Society
2017 – 2018 Program Committee, SRBR 2018 Symposium
2017 – 2018 Junior Faculty Workshop Committee, SRBR 2018 Symposium
2017 Group Discussion Leader, Gordon Research Seminar on Chronobiology
2015 – 2020 Chair, SRBR Logo Committee for 2016, 18, 20 Meeting
2015 – 2017 Member, SRBR Membership Committee

Editorial boards

2023 – Associate Editor, Nature Partner Journals *Biological Timing and Sleep*
2022 – Associate Editor, *FEBS Letters*

**Funding**

NIH / NIGMS R35 GM141849 5/1/2021 – 4/30/2026
Title: Structures and mechanisms of circadian rhythms from cyanobacteria to humans
This project aims to understand the mechanistic basis for circadian timekeeping in diverse species using biochemical, cell-based and structural biological approaches.

Administrative supplement to NIH / NIGMS R35 GM141849 8/1/2023 – 4/30/2026
Funding was provided to support diversity in biomedical science.

**Major Publications**

* Equal contributions

Δ Co-corresponding authors


Philpott, J.M., Freeberg, A.M., Park, J., Lee, K., Ricci, C.G., Hunt, S.R., Narasimamurthy, R., Segal, D.H., Robles, R., Cai, Y.D., Tripathi, S., McCammon, J.A., Virshup, D.M., Chiu, J.C., Lee, C.Δ, Partch, C.L.Δ (2023) PERIOD phosphorylation leads to feedback inhibition of CK1 activity to control circadian period. ***Molecular Cell***, 83: 1677-1692

Swan, J.A.*, Sandate, C.R.*, Chavan, A., Freeberg, A.M., Etwaru, D., Ernst, D.C., Palacios, J.G., Golden, S.S., LiWang, A., Lander, G.C.Δ, Partch, C.L.Δ (2022) Coupling of distant ATPase domains in the circadian clock protein KaiC. ***Nature Structural and Molecular Biology*** 29: 759-766

Chavan, A.*, Swan, J.A.*, Heisler, J.*, Sancar, C., Ernst, D.C., Fang, M., Palacios, J.G., Spangler, R.K., Bagshaw, C.R., Tripathi, S., Crosby, P., Golden, S.S., Partch, C.L.Δ, LiWang, A.Δ (2021) Reconstitution of an intact clock reveals mechanisms of circadian timekeeping. ***Science*** 374(6564): eabd4453

Parico, G.C.G., Perez, I., Fribourgh, J.L., Hernandez, B.N., Lee, H.-W., Partch, C.L. (2020) The CRY1 tail controls circadian timing by regulating its association with CLOCK:BMAL1. ***Proceedings of the National Academy of Sciences USA*** 117: 27971-27979

Fribourgh, J.L.*, Srivastava, A.*, Sandate, C.R.*, Michael, A.K., Hsu, P.L., Rakers, C., Nguyen, L.T., Torgrimson, M., Parico, G.C., Tripathi, S., Zheng, N., Lander, G.C., Hirota, T., Tama, F.Δ, Partch, C.L.Δ (2020) Dynamics at the serine loop underlie differential affinity of cryptochromes for CLOCK:BMAL1 to control circadian timing. ***eLife***, doi: 10.7554/eLife.55275

Philpott, J.M.*, Narasimamurthy, R.*, Ricci, C.G.*, Freeberg, A.M., Hunt, S.R., Yee, L., Pelofsky, R.S., Tripathi, S., Virshup, D.M.Δ, Partch, C.L.Δ (2020) Casein kinase 1 dynamics underlie substrate selectivity and the PER2 circadian phosphoswitch. ***eLife***, doi: 10.7554/eLife.52343

Gustafson, C.L., Parsley, N.C., Asimgil, H., Lee, H.W., Ahlbach, C., Michael, A.K., Xu, H., Williams, O.L., Davis, T.L., Liu, A.C., Partch, C.L. (2017) A slow conformational switch in the BMAL1 transactivation domain modulates circadian rhythms, ***Molecular Cell***, 66: 447-457

Tseng, R.*, Goularte, N.F.*, Chavan, A.*, Luu, J., Cohen, S.E., Chang, Y.G., Heisler, J., Li, S., Michael, A.K., Tripathi, S., Golden, S.S., LiWang, A.Δ, Partch, C.L.Δ (2017) Structural basis of the day/night transition in the cyanobacterial circadian clock, ***Science***, 355: 1174-1180

Michael, A.K., Fribourgh, J.L., Chelliah, Y., Sandate, C.R., Hura, G.L., Schneidman-Duhovny, D., Tripathi, S., Takahashi, J.S., Partch, C.L. (2017) Formation of a repressive complex in the circadian clock is mediated by the secondary pocket of cryptochromes. ***Proceedings of the National Academy of Sciences USA***, 114: 1560-65

Xu, X.*, Gustafson, C.L.*, Sammons, P.J., Khan, S.K., Parsley, N.C., Ramanathan, C., Lee, H.-W., Liu, A.C.Δ, Partch, C.L.Δ (2015) Cryptochrome 1 regulates the circadian clock through dynamic interactions with the BMAL1 C-terminus. ***Nature Structural and Molecular Biology*** 22: 476-84

**Peer Reviewed Journal Articles and Preprints**

* Equal contributions

Δ Co-corresponding authors

40. Harold, R.*, Tulsian, N.K.*, Narasimamurthy, R., Yaitanes, N., Hernandez, M.A., Lee, H.-W., Virshup, D.M. Δ, Partch, C.L.Δ (2023) Isoform-specific changes in the disordered C-terminus of Casein Kinase 1δ differentially inhibit kinase activity. ***bioRxiv*** https://doi.org/10.1101/2023.04.24.538174

39. Lamberti, M.L., Spangler, R.K., Cerceira, V., Ares, M., Rivollet, L., Ashley, G.E., Ramos Coronado, A., Tripathi, S., Spiousas, I., Ward, J.D., Partch, C.L., Benard, C.Y., Goya, M.G., Golmbek, D.A. (2023) Regulation of the circadian clock in *C. elegans* by clock gene homologs kin-20 and lin-42. ***bioRxiv*** https://doi.org/10.1101/2023.04.13.536481

38. Crosby, P., Goularte, N.F., Sharma, D., Chen, E., Parico, G.C.G., Philpott J.M., Harold, R., Gustafson, C.L., Lee, H.-W., Partch (2022) CHRONO participates in multi-modal repression of circadian transcriptional complexes. ***bioRxiv*** https://doi.org/10.1101/2022.10.04.510902

37. Wu, T., Yu, J.C., Suresh, A., Gale-Day, Z.J., Alteen, M.G., Woo, A.S., Millbern, Z., Johnson, O.T., Carroll, E.C., Partch, C.L., Fourches, D., Vinueza, N.R., Vocadlo, D.J., Gestwicki, J.E. (2023) Conformationally responsive dyes enable protein-adaptive differential scanning fluorimetry. ***Nature Biotechnology***, accepted; ***bioRxiv*** https://doi.org/10.1101/2023.01.23.525251

36. Chavan, A., Heisler, J., Chang, Y.-G., Golden, S.S., Partch, C.L., LiWang, A. (2023) Protocols for ***in vitro*** reconstitution of the cyanobacterial clock. ***Biopolymers***, https://doi.org/10.1002/bip.23559

35. Michael, A.K.*, Stoos, L.*, Crosby, P., Eggers, N., Nie, X.Y., Makasheva, K., Minnich, M., Healy, K.L., Weiss, J., Kempf, G., Cavadini, S., Kater, L., Seebacher, J., Vecchia, L., Chakraborty, D., Isbel, L., Grand, R.S., Andersch, F., Fribourgh, J.L., Schübeler, D., Zuber, J., Liu, A.C., Becker, P.B., Fierz, B., Partch, C.L., Menet, J.S., Thomä, N.H. (2023) Cooperation between bHLH transcription factors and histones for DNA access. ***Nature***, 619: 385-393

- Featured in Murawska, M. et al. (2023) Pioneers conquer core histones at the chromatin frontier. ***Nat Struct Mol Biol***, 30: 1050-1053

34. Philpott, J.M., Freeberg, A.M., Park, J., Lee, K., Ricci, C.G., Hunt, S.R., Narasimamurthy, R., Segal, D.H., Robles, R., Cai, Y.D., Tripathi, S., McCammon, J.A., Virshup, D.M., Chiu, J.C., Lee, C.Δ, Partch, C.L.Δ (2023) PERIOD phosphorylation leads to feedback inhibition of CK1 activity to control circadian period. ***Mol Cell***, 83: 1677-1692

33. Swan, J.A.*, Sandate, C.R.*, Chavan, A., Freeberg, A.M., Etwaru, D., Ernst, D.C., Palacios, J.G., Golden, S.S., LiWang, A., Lander, G.C.Δ, Partch, C.L.Δ (2022) Coupling of distant ATPase domains in the circadian clock protein KaiC. ***Nat Struct Mol Biol*** 29: 759-766

32. Bagnall, J.S.*, Koch, A.A.*, Smyllie, N.J., Begley, N., Adamson, A.D., Fribourgh, J.L., Spiller, D.G., Meng, Q.-J., Partch, C.L., Strimmer, K., House, T.A., Hastings, M.H., Loudon, A.S.I. (2022) Quantification of circadian interactions and protein abundance defines a mechanism for operational stability of the circadian clock. ***eLife,*** doi: 10.7554/eLife.73976

31. Smyllie, N.J., Bagnall, J., Koch, A.A., Niranjan, D., Polidarova, L., Chesham, J.E., Partch, C.L., Chin, J.W., Loudon, A.S.I., Hastings, M.H. (2021) Cryptochrome proteins regulate the circadian intra-cellular behavior and localization of PER2 in mouse suprachiasmatic nucleus neurons. ***Proc Natl Acad Sci USA***,119(4):e2113845119.

30. Shen, Y., Wang, W., Endale, M., Francey, L.J., Harold, R.L., Hammers, D.W., Huo, Z., Partch, C.L., Hogenesch, J.B., Wu, Z.-H., Liu, A.C. (2021) NF-κB modifies the mammalian circadian clock through interaction with the core clock protein BMAL1. ***PLoS Genet*** 17(11):e1009933

29. Chavan, A.*, Swan, J.A.*, Heisler, J.*, Sancar, C., Ernst, D.C., Fang, M., Palacios, J.G., Spangler, R.K., Bagshaw, C.R., Tripathi, S., Crosby, P., Golden, S.S., Partch, C.L.$^{\Delta}$, LiWang, A.$^{\Delta}$ (2021) Reconstitution of an intact clock reveals mechanisms of circadian timekeeping. ***Science*** 374(6564): eabd4453

· Featured in Rust, M.J. (2021) Biological rhythms: The suspended animation clock. ***Curr Biol*** 31: R1513-R1534

28. Koronowski, K.B., Greco, C.M., Huang, H., Kim, J.-K., Fribourgh, J.L., Crosby, P.C., Partch, C.L., Qiao, F., Zhao, Y., Sassone-Corsi, P. (2021) Ketogenesis impact on liver metabolism revealed by proteomics of lysine β-hydroxybutyrylation. ***Cell Reports*** 35(5):109487

27. Chan, A.B., Parico, G.C.G., Fribourgh, J.L., Ibrahim, L.H., Bollong, M.J., Partch, C.L., Lamia, K.A. (2021) ***CRY2*** missense mutations suppress P53 and enhance cell growth. ***Proc Natl Acad Sci USA*** 118(27): e2101416118

26. Parico, G.C.G., Perez, I., Fribourgh, J.L., Hernandez, B.N., Lee, H.-W., Partch, C.L. (2020) The CRY1 tail controls circadian timing by regulating its association with CLOCK:BMAL1. ***Proc Natl Acad Sci USA*** 117: 27971-27979

25. Fribourgh, J.L.*, Srivastava, A.*, Sandate, C.R.*, Michael, A.K., Hsu, P.L., Rakers, C., Nguyen, L.T., Torgrimson, M., Parico, G.C., Tripathi, S., Zheng, N., Lander, G.C., Hirota, T., Tama, F.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2020) Dynamics at the serine loop underlie differential affinity of cryptochromes for CLOCK:BMAL1 to control circadian timing. ***eLife***, doi: 10.7554/eLife.55275

24. Philpott, J.M.*, Narasimamurthy, R.*, Ricci, C.G.*, Freeberg, A.M., Hunt, S.R., Yee, L., Pelofsky, R.S., Tripathi, S., Virshup, D.M.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2020) Casein kinase 1 dynamics underlie substrate selectivity and the PER2 circadian phosphoswitch. ***eLife***, doi: 10.7554/eLife.52343

· Featured in NIH Director's Blog "Early riser or night owl? New study may help to explain the difference" (Feb. 25, 2020)

23. Narasimamurthy, R., Hunt, S.R., Lu, Y., Fustin, J.M., Okamura, H., Partch, C.L., Kim, J.K., Forger, D.B., Virshup, D.M. (2018) CK1**d**/**e** protein kinases prime the PER2 circadian phosphoswitch. ***Proc Natl Acad Sci USA*** 115: 5986-91

22. Fong, J.C., Rogers, A., Michael, A.K., Parsley, N.C., Cornell, W., Lin, Y., Singh, P.K., Hartmann, R., Drescher, K., Vinogradov, E., Dietrich, L., Partch, C.L.$^{\Delta}$, Yildiz, F.H.$^{\Delta}$ (2017) Structural dynamics of RbmA governs plasticity of *Vibrio cholerae* biofilms, ***Elife*** 6:e26163 DOI: 10.7554/eLife.26163

· Featured in Pierrat, X. and Persat, A. (2017) Biofilms: Flipping the switch. ***Elife*** 6:e31082; York, A. (2017) The architect of the biofilm. ***Nat Rev Microb***, doi:10.1038/nrmicro.2017.127

21. Gustafson, C.L., Parsley, N.C., Asimgil, H., Lee, H.W., Ahlbach, C., Michael, A.K., Xu, H., Williams, O.L., Davis, T.L., Liu, A.C., Partch, C.L. (2017) A slow conformational switch in the BMAL1 transactivation domain modulates circadian rhythms, ***Molecular Cell***, 66: 447-457

· Cover Article; featured in Narasimamurthy, R. and Virshup, D.M. (2017) A flick of the tail keeps the circadian clock in line. ***Molecular Cell*** 66: 437-438; Miura, G. (2017) Switching periods. ***Nat Chem Biol*** 13: 693.

20. Tseng, R.*, Goularte, N.F.*, Chavan, A.*, Luu, J., Cohen, S.E., Chang, Y.G., Heisler, J., Li, S., Michael, A.K., Tripathi, S., Golden, S.S., LiWang, A.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2017) Structural basis of the day/night transition in the cyanobacterial circadian clock, ***Science***, 355: 1174-1180

· Featured in York, A. (2017) The tick-tock of circadian clocks. ***Nature Rev Micro*** 15: 256

19. Michael, A.K., Fribourgh, J.L., Chelliah, Y., Sandate, C.R., Hura, G.L., Schneidman-Duhovny, D., Tripathi, S., Takahashi, J.S., Partch, C.L. (2017) Formation of a repressive complex in the circadian clock is mediated by the secondary pocket of cryptochromes. ***Proc Natl Acad Sci USA***, 114: 1560-65

18. Militi, S.*, Maywood, E.S.*, Sandate, C.R., Chesham, J.E., Barnard, A.R., Parsons, M.J., Joynson, G., Partch, C.L., Hastings, M.H., Nolan, P.M. (2015) The ***early doors*** (***Edo***) mutant mouse reveals the importance of PER2 PAS domain structure for circadian pacemaking, ***Proc Natl Acad Sci USA*** 113: 2756-61

17. Xu, X.*, Gustafson, C.L.*, Sammons, P.J., Khan, S.K., Parsley, N.C., Ramanathan, C., Lee, H.-W., Liu, A.C.$^{\Delta}$, Partch, C.L.$^{\Delta}$ (2015) Cryptochrome 1 regulates the circadian clock through dynamic interactions with the BMAL1 C-terminus. ***Nature Structural and Molecular Biology*** 22: 476-84

· Cover Article; featured in Hui, K.Y. and Ripperger, J.A. (2015) Grab the wiggly tail: new insights into the dynamics of circadian clocks, ***Nature Structural and Molecular Biology*** 22: 436-36

16. Michael, A., Harvey, S., Sammons, P.J., Anderson, A.P., Kopalle, H.M., Banham, A.H., Partch, C.L. (2015) Cancer/testis antigen PASD1 silences the circadian clock. Molecular Cell 15: 743-54

· Focus of Quanta Magazine feature, “How the Body’s Trillions of Clocks Keep Time” –Nikki Greenwood

15. Guo, Y., Scheuermann, T.H., Partch, C.L., Tomchick, D.R., Gardner, K.H. (2015) Coiled-coil coactivators play a structural role in mediating interactions in hypoxia-inducible factor heterodimerization. ***J Biological Chemistry*** 290: 7707-21

14. Mukherjee, S., Zheng, H., Derebe, M., Partch, C.L., Rollins, D., Rizo, J., Jiang, Q.-X., Hooper, L.V. (2014) Antibacterial membrane attack by a pore-forming intestinal C-type lectin. ***Nature*** 505: 103-7

13. Guo, Y., Partch, C.L., Key, J., Card, P.B., Wurdak, H., Gardner, K.H. (2013) Regulating the ARNT-TACC3 axis: multiple approaches to manipulating protein-protein interactions with small molecules. ***ACS Chemical Biology*** 8: 626-35

12. Huang, N.*, Chelliah, Y.*, Taylor, C.A., Yoo, S.H., Shan, Y., Partch, C.L. Green, C., Zhang, H. Δ, Takahashi, J.S. Δ (2012) Crystal structure of the heterodimeric CLOCK:BMAL1 transcriptional activator complex of the mammalian circadian clock. ***Science*** 337: 189-94

· Featured in Crane, B. (2012) Nature's Intricate Clockwork. ***Science*** 337:165-166

11. Partch, C.L. and Gardner, K.H. (2011) Coactivators necessary for transcriptional output of the hypoxia inducible factor, HIF, are directly recruited by ARNT PAS-B. ***Proc Natl Acad Sci USA*** 108: 7739-44

10. Lehotzky, R.E.*, Partch, C.L.*, Mukherjee, S., Cash, H., Goldman, W.E., Gardner, K.H., Hooper, L.V. (2010) Molecular basis for peptidoglycan recognition by a bactericidal lectin. ***Proc Natl Acad Sci USA*** 107: 7722-7

9. Partch, C.L., Card, P.B., Amezcua, C.A., Gardner, K.H. (2009) Molecular basis of coiled coil coactivator recruitment by the aryl hydrocarbon receptor nuclear translocator (ARNT). ***J Biological Chemistry*** 284: 15184-92

8. Mukherjee, S.*, Partch, C.L.*, Lehotzky, R.E., Whitham, C., Chu, H., Bevins, C., Gardner, K.H., Hooper, L.V. (2009) Regulatio***n of C-type lectin antimicrobial activity by a flexible N-terminal propeptide.*** J Biological Chemistry 284: 4881-86

7. Öztürk, N., Kao, Y.T., Selby, C.P., Kavakli, I.H., Partch, C.L., Zhing, D., Sancar, A. (2008) Purification and characterization of a Type III Photolyase from ***Caulobacter crescentus***. ***Biochemistry*** 47: 10255-61

6. Huang, Y., Baxter, R., Smith, B.S., Partch, C.L., Colbert, C.L., Deisenhofer, J. (2006) Crystal structure of cryptochrome 3 from Arabidopsis thaliana: a novel MTHF binding mode and implications for photolyase activity. ***Proc Natl Acad Sci USA*** 103: 17701-06

5. Partch, C.L., Shields, K.F., Thompson, C.L., Selby, C.P., Sancar, A. (2005) Posttranslational regulation of the mammalian circadian clock by cryptochrome and protein phosphatase 5. ***Proc Natl Acad Sci USA*** 103: 10467-72

4. Partch, C.L., Clarkson, M.W., Özgür, S., Lee, A.L., Sancar, A. (2005) Role of structural plasticity in signal transduction by the cryptochrome blue-light photoreceptor. ***Biochemistry*** 44: 3795-3805

3. Thompson, C.L.*, Selby, C.P.*, Partch, C.L., Plante, D.T., Thresher, R.J., Araujo, F., Sancar, A. (2004) Further evidence for the role of cryptochromes in retinohypothalamic photoreception/ phototransduction. ***Brain Research: Molecular Brain Research*** 122: 158-66

2. Carr, D.W., Fujita, A., Stentz, C.L., Liberty, G.A., Olson, G.A., Narumiya, S. (2001) Identification of sperm-specific proteins that interact with A-Kinase anchoring proteins in a manner similar to the Type II regulatory subunit of PKA. ***J Biological Chemistry*** 276: 17332-38

1. Kasyapa, C.S., Stentz, C.L., Davey, M.P., Carr, D.W. (1999) Regulation of IL-15-stimulated TNFα production by Rolipram. ***J Immunology*** 163: 2836-43

**Invited reviews, commentaries and book chapters**

22. Fang, M., LiWang, A., Golden, S.S., Partch, C.L. (2024) The inner workings of an ancient biological clock. ***Trends in Biochemical Sciences***, Accepted doi: 10.1016/j.tibs.2023.12.007

21. Rojas, B.L., Partch, C.L., Vazquez-Rivera, E., Bradfield, C.A. (2023) Dimerization rules of mammalian PAS proteins. ***J Mol Biol*** Invited Review, Accepted doi: 10.1016/j.jmb.2023.168406

20. Sharma, D. and Partch, C.L. (2023) PAS domains at the nexus of the mammalian circadian clock. ***J Mol Biol*** Invited Review, Accepted doi: 10.1016/j.jmb.2023.168341

19. Philpott, J.M., Torgrimson, M.R., Harold, R.L., and Partch, C.L. (2021) Biochemical mechanisms of period control within the mammalian circadian clock. ***Seminars in Cell and Developmental Biology*** S1084-9521(21)00085-9 doi: 10.1016/j.semcdb.2021.04.012

18. Parico, G.C.G. and Partch, C.L. (2020) The tail of cryptochromes: an intrinsically disordered cog within the mammalian circadian clock. ***Cell Commun Sig*** 18: 182

17. Crosby, P.R. and Partch, C.L. (2020) New insights into post-transcriptional regulation of mammalian circadian timekeeping. ***J Cell Science***, 133: jcs241174

16. Partch, C.L. (2020) Orchestration of circadian timing by macromolecular protein assemblies. ***J Molecular Biology*** 432: 3426-3448

15. Ceh-Pavia, E. and Partch, C.L. (2019) Flipping behavior with the flip of a translational switch. ***Proc Natl Acad Sci USA***, 115: 13151-13153

14. Swan, J.A., Golden, S.S., LiWang, A., Partch, C.L. (2018) The core circadian clock in cyanobacteria: structure and mechanism. ***J Biological Chemistry*** MiniReview, 293:5026-5034

13. Fribourgh, J.L. and Partch, C.L. (2017) Assembly and function of bHLH-PAS complexes. ***Proc Natl Acad Sci USA***, 114: 5330-5332

12. Michael, A.K.*, Fribourgh, J.L.*, Van Gelder, R.N., Partch, C.L. (2016) Animal cryptochromes: Divergent roles in light perception, circadian timekeeping and beyond. ***Photochemistry and Photobiology*** – Special Issue in honor of 2015 Nobel Laureate in Chemistry Aziz Sancar, 93: 128-140

11. Michael, A.K., Asimgil, H., Partch, C.L. (2015) Cytoplasmic BMAL1 moonlights as a translation factor. ***Trends in Biochemical Sciences*** 40: 489-90

10. Gustafson, C.L. and Partch, C.L. (2015) Emerging models for the molecular basis of mammalian circadian timing. ***Biochemistry*** 54: 134-49

9. Huynh, K. and Partch, C.L. (2015) Analysis of protein stability and ligand interactions by thermal shift assay. ***Current Protocols in Protein Science*** 79:28.9

8. Kopalle, H.M. and Partch, C.L. (2014) An ImPERfect link to cancer? ***Cell Cycle*** 13:507

7. Partch, C.L., Green, C.B., Takahashi, J.S. (2014) Molecular architecture of the mammalian circadian clock. ***Trends in Current Biology*** 24: 90-9

6. Motta-Mena, L.B., Partch, C.L., Gardner, K.H. (2010) The three Rs of transcription: recruit, retain, recycle. ***Molecular Cell*** 40: 855-58

5. Partch, C.L. and Gardner, K.H. Coactivator recruitment: a new role for PAS domains in transcriptional regulation by the bHLH-PAS family (2010) ***J Cell Physiology*** 223: 553-7

4. Öztürk, N., Song, S., Özgür, S., Selby, C.P., Morrison, L., Partch, C.L., Zhong, D., Sancar, A. (2007) Structure and function of animal cryptochromes. ***Cold Spring Harbor Symposium on Clocks and Rhythms*** 72: 119-131

3. Partch, C.L. and Sancar, A. (2005) Photochemistry and photobiology of cryptochrome blue-light photopigments: The search for a photocycle. ***Photochemistry and Photobiology*** 81: 1291-1304
- Cover Article

2. Partch, C.L. and Sancar, A. (2005) Cryptochromes and circadian photoreception in animals. Methods in Enzymology, Circadian Rhythms, Young, M.W. ed., Elsevier Science, Vol. 393, p. 724-743

1. Partch, C.L. and Sancar, A. (2004) DNA Photolyase, ***Encyclopedia of Biological Chemistry***, Lennarz, W. and Lane, M.D., eds., Elsevier Science

**Lay publications**

2. "Nobel winners identified molecular 'cogs' in the biological clocks that control our circadian rhythms." The Conversation, Oct. 2, 2017. http://bit.ly/2xOsTZW

1. "Scientists are unraveling the mystery of your body's clock – and soon may be able to reset it." The Conversation, Sept. 17, 2017. http://bit.ly/2xcw1v3

**Molecular animations**

Swan, J., Lopez-Rivera, F., Iwasa, J., Partch, C.L. (2023) KaiC and the cyanobacterial circadian clock. https://vimeo.com/789040719