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BIOGRAPHICAL SKETCH

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NAME: Dunlap, Jay C

eRA COMMONS USER NAME (credential, e.g., agency login): JCDUNLAP

POSITION TITLE: Nathan Smith Professor of Genetics and Chairman of Molecular & Systems Biology

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of Washington, Seattle, WA | BS & BS | 1974 | Chemistry/Oceanography |
| Harvard University, Cambridge, MA | AM | 1975 | Biology |
| Harvard University, Cambridge, MA | PhD | 1979 | Biology |
| University of California, Santa Cruz | PPhD | 1979-1983 | Genetics |

# A. Personal Statement

My research has focused on understanding the molecular basis of circadian rhythms in the model system Neurospora, and more recently on translating insights gained from Neurospora into understanding mammalian circadian clocks. Because entrainment of rhythms is so closely tied to photobiology, I have also been drawn into studying the molecular bases of photoreception in fungi. Most recently as one of the largest labs working on filamentous fungi we have led efforts to develop functional genetic and genomic tools to exploit these organisms. The circadian system is one of the overarching physiological control mechanisms in humans and, in fact, in nearly all eukaryotes.  Dysfunction in the circadian system lies at the basis of some sleep and psychiatric disorders as well as a variety of metabolic disorders.

I benefitted enormously from mentoring as a junior scientist and have tried to pass this forward. Over the years I have trained a number of undergraduate and graduate students and 33 postdoctoral fellows, 19 of whom presently hold positions at academic institutions at levels ranging from assistant professor to department chair. Outside of my lab, in my capacity as chairman and also as a more senior scientist in my flelds, I have helped to mentor more than a dozen scientists junior to me including several now in junior faculty positions, two from my department who have gone off to become department chairs, and one who was elected to the National Academy.

# B. Positions and Honors

#### Positions and Employment

1984 - 1989 Assistant Professor of Biochemistry, Dartmouth Medical School

1990 - 1994 Associate Professor of Biochemistry, Dartmouth Medical School

1994 - 1999 Professor of Biochemistry, Dartmouth Medical School

1999 - 2016 Professor and Inaugural Chair, Dept. Genetics, Geisel School of Medicine at Dartmouth

2010 named Nathan Smith Professor

2016- Professor and Inaugural Chair, Dept. Molecular & Systems Biology, Geisel School of Medicine at Dartmouth

**Other Experience and Professional Memberships**

Membership: Genetic Society of America, American Society for Microbiology, American Society for Cell Biology. Society for Research on Biological Rhythms, AAAS

National Institutes of Health: National Advisory Council for General Medical Sciences, 2000 – 2004, 2011; Board of Scientific Advisors, Lab. of Molecular and Cellular Regulation, NIMH Intramural Prog., 1999; Microbial Genetics and Physiology Study Section; Ad Hoc reviews (Genetics, Microbial Genetics and Physiology, Special Study Sections on Circadian Rhythms and Sleep), ZRG1 NCF-D, EUREKA (2008), NIH Director's Pioneer Awards (2008, 2009; chair, 2011), NIH New Innovator 2012; NIGMS Select Committee for PSI Evaluation 2014; NIGMS Co-chair select committee to evaluate P50 Systems Biology Center program 2015

Editorial Activities: co-Editor-in-Chief, Advances in Genetics (1995 - ); Editor, Eukaryotic Cell (ASM Press) (2001 - 2011), editorial boards, J. Biological Rhythms (1994 – 2001; 2014 -); G3 (2011 - )

Meetings: 1991 - co-Organizer, 16th Biennial Fungal Genetics Conf.; 1995 - co-Organizer, APS meeting, The Genetics and Physiology of Circadian Rhythms; 1998 - Chair, Cellular and Molecular Mycology Gordon Conference; 2007-co-Proposer 72st Cold Spring Harbor Symposium: Circadian Rhythms; 2008; co-Organizer, Keystone Sleep meeting; 2009, co-Organizer, 25th Biennial Fungal Genetics Conf.

National Science Foundation: Regular Member - NSF Grant Review Panel on Microbial Genetics (1989 - 1992); Ad Hoc reviewer; NSF Center for Biological Timing - External Advisory Committee, 1991 - 2002

UK Medical Research Council, outside reviewer for the Laboratory of Molecular Biology, Neurobiology Division, Cambridge. 2004

External Advisory Committee, UO1 GM61388 "Pharmacogenetics of Phase II Drug Metabolizing Enzymes, Mayo Clinic, 2004-14 , P01 NS39546-01 "Coordination of Circadian Physiology”, Texas A&M

Scientific Community: Society for Research on Biological Rhythms (600+ members) - President, (1998 – 2000) Treasurer (1992 – 1994); Comm. to Sequence Neurospora - chair (1996-2000); *Neurospora* Policy Committee - Chair, 1993 – 1995; Fungal Genetics Policy Committee (1991-1999); Genetics Society of America: Board of Directors (2009 – 2012); FASEB: Board Of Directors (2012 – 2014); Selection Comm. for Honma International Prize in Chronobiology 2012-2016

**Honors and Awards**

1974 Phi Beta Kappa, Phi Lambda Upsilon (National Chemistry Honorary)

1974 Graduation, separate degrees in Chemistry and Oceanography, Magna cum Laude in each

1980 Damon Runyon - Walter Winchell Fellowship

1983 National Research Service Award, NIH

1991 Honma International Prize For Biological Rhythms Research - a prize of ¥1,000,000, awarded biennially to a scientist under 40 for "exceptional contributions in the field of circadian rhythms"

1992 - 1997 Senior Scientist Award, National Institute of Mental Health

1998 MERIT award, NIGMS

2005 (first) recipient of Genetics Society of America Robert L. Metzenberg Award

2009 George W. Beadle Medal, Genetics Society of America

2009 elected to the National Academy of Sciences, Genetics section

2010 elected fellow of AAAS

2010 elected to the American Academy of Microbiology

2013 Fellow, Texas A&M University Institute for Advanced Studies

# C. Contributions to Science

1. **General**: When I began my own research as an assistant professor in 1984 there were a few genes identified thorough classical forward screens in Chlamydomonas, Neurospora, and Drosophila but no clock genes were cloned. My goal was to describe the circadian system in the language of genetics and biochemistry, i.e. all the things in the cell required for full circadian characteristics and how they worked together to yield (1) a sustained oscillation (2) with a period of about a day under constant conditions, (3) resettable by light and temperature cues, and (4) compensated against changes in ambient temperature and nutrition. I asserted (controversially but correctly as it turned out) that single cells including those in mammals were capable of executing all circadian characteristics. We conceptually broke the problem into 3 parts: (1) Mechanism, meaning identification of the parts required for the oscillation itself and its environmental compensation, and how they work together to keep time; (2) Input, meaning the components and the mechanism by which light and temperature cues reset the clock; (3) Output, meaning the pathways and mechanisms through which the core oscillator controls the metabolism of the cell. We have been successful in all three of these goals; the third area, output, was separated and became the focus of a long term colleague, Jennifer Loros.

One grant reviewer referred to the pre-molecular era of rhythms science as the era of “spoon-bending”; indeed not all the science was good. As a part of pulling the field together I have tried to take seriously efforts at reviewing the literature to identify emerging common themes to this common biology of circadian rhythmicity, thus focusing not just on work in Neurospora but rather on work in molecular rhythms written large(r). Although reviews are not as sexy as primary papers, and they are certainly labors of love, they can be very important and influential if done well. Although a number have garnered many citations, two stand out.

a. Dunlap, Jay C. Molecular Bases of Circadian Oscillators. 1999. **Cell** 96: 271 – 290.

This is the most highly cited article on “circadian rhythms” with >2400 citations listed by Google Scholar, not counting the translations into several languages.

b. **Chronobiology: Biological Timekeeping**, 382 pages, 278 illustrations, ISBN 0-87893-149-X. Jay C. Dunlap, Jennifer J. Loros, and P. J. DeCoursey, April 2003, Sinauer Associates. At the time, it was the first textbook on circadian biology to be published in 18 years and the first to embrace the genetic and molecular era. Royalties were donated to the Society for Research on Biological Rhythms.

 2. **Clock** **Mechanism:** Work on core mechanism comprises a major aspect of my work. We are credited with cloning the second clock gene to be cloned, *frq* (1986, just after Drosophila *per*); with proving (as distinct from proposing) that the core oscillator requires negative feedback and autoregulation of/by the products of clock genes (1994); first identifying PAS:PAS heterodimers as transcriptional activators in the core circadian oscillator and providing the first correct model of a single step negative feedback loop directly connecting activation and repression (both 1997); demonstrating contemporaneous with animal circadian researchers the importance of phosphorylation of clock proteins and the existence of interconnected feedback loops surrounding the core (2000); providing the 1st mechanistic entre to temperature compensation (2009); demonstrating that the core feedback loops closes through phosphorylation-mediated inactivation of negative elements rather than through phosphorylation-mediated turnover of those elements (2015).

a. Aronson, B., Johnson, K., J.J. Loros, and **Jay C. Dunlap**. 1994. Negative Feedback Defining a Circadian Clock: Autoregulation of the Clock Gene *frequency*, **Science,** 263, 1578 – 1584**.**

b. Crosthwaite, S., **Dunlap, Jay C. and J. J. Loros**. 1997. Neurospora *wc-1* and *wc-2*: Transcription, Photoresponses, and the Origins of Circadian Rhythmicity. **Science** 276, 763 - 769.

c. Mehra A, Shi M, Baker, C.L., Colot, H. V., Loros JJ, Dunlap JC. 2009. A role for Casein Kinase 2 in the mechanism underlying circadian temperature compensation in Neurospora. **Cell** 137: 749 – 760.

d. Larrondo, L. L., Olivares-Yañez, C., Baker, C. L., Loros, J. J., and Dunlap, J. C. 2015. Decoupling circadian clock protein turnover from circadian period determination. **Science** 347: 476-477 AND DOI: 10.1126/science.1257277

3. **Circadian Input and Photobiology**: A defining characteristic of circadian systems is that, while their oscillation will continue in the absence of environmental cues, their phase (i.e. when peaks and troughs occur) must be able to be reset by environmental cues. This is the whole basis of jet lag, and also of every organism’s ability to adapt to changing seasons. And, as this implies, the phase (time of day) at which clock components peak defines aspects of their resetting mechanism. Clearly it is impossible to do meaningful mechanistic work on input before any components are identified, but once the product of the *frq* was proven to be a clock component and its amount in the cell a state variable of the oscillator (see above; Science, 1994), then we had a handle. Levels of *frq* mRNA peak in the morning and we showed that the Neurospora clock is reset through acute induction of *frq* transcription (1995). In this article correctly predicted that the Drosophila clock, in which *per* gene expression peaks at night, would be reset by light-activated turnover of PER. Mammalian clocks are reset in the same way as Neurospora, through light-induction of clock genes (1997). Temperature influences the amount of FRQ at the level of translation, providing the 1st mechanism for temperature resetting. We identified the photoreceptor as WC-1, a dual-function protein that is also the circadian activator in the dark; it is the founding member of the family of proteins comprising the principal photoreceptors in the entire Kingdom of Fungi.

a. Crosthwaite, S., Loros, J. J. and Jay C. Dunlap. 1995. Light-Induced Resetting of a Circadian Clock is Mediated by a Rapid Increase in frequency Transcript, **Cell** 81, 1003 - 1012

b. Shigeyoshi, Y., Taguchi, K., Yamamoto, S., Takeida, S., Yan, L., Tei, H., Moriya, S., Shibata, S., Loros, J. J. , Dunlap, J. C. and Okamura, H. 1997. Light-induced Resetting of a Mammalian Circadian Clock is Associated with Rapid Induction of the *mPer1* Transcript. **Cell** 91, 1043 - 1053

c. Liu, Y., Merrow, M., Loros, J. J. and Jay. C. Dunlap. 1998. How Temperature Changes Reset a Circadian Oscillator, **Science** 281, 825 - 829.

d. Froehlich A. C., Liu, Y., Loros, J. J., and Dunlap J.C. 2002. White Collar-1, a circadian blue light photoreceptor, binding to the *frequency* promoter. **Science** 297, 815-819.

4. **Technical and methodological Innovation**: While information and knowledge are advanced through experimentation, experimentation is advanced through technological innovation. As my lab grew in size it was plain that we needed to assume more responsibility for this. Our initial contribution (1991) was the first gene replacement strategy for Neurospora (or filamentous fungi), and later when in part through our hard fund-raising work Neurospora became the first filamentous fungus to have its genome sequenced (2002), we went back and perfected gene replacements so that now we can do replacements within two weeks with >98% accuracy; essential genes are also sheltered (2006). Using this we spearheaded the effort to knock out all ~10,000 genes in the genome. These knockouts are all deposited in the Fugal Genetics Stock Center and comprise a resource that has seen tremendous use. We also spearheaded construction of a high density SNP map. Lastly we tamed luciferase for Neurospora by addressing codon bias and thereby increasing expression by 4-5 log orders (!). This has revolutionized analysis of circadian gene expression and allowed correction of several errors in the literature resulting from conflation of circadian output with core oscillator function. Recently we have also begun work on the fungal pathogen Aspergillus fumigatus, both describing its photobiology and a widely used method for gene manipulations using CRISPR.

a. Colot H.V., Park, G., Turner G.E., Ringelberg C., Crew C.M., Litvinkova L., Weiss R.L., Borkovich K.A., Dunlap J. C. 2006. A high-throughput gene knockout procedure for Neurospora reveals functions for multiple transcription factors. **Proc Natl Acad Sci U S A.** 103:10352-10357.

b. Dunlap, J. C., *et al.* 2007. Enabling a community to dissect an organism - Overview of The Neurospora Functional Genomics Project **Adv. Genetics** 57, 49 – 96.

c. Gooch V, Mehra A, Larrondo L, Fox J, Touroutoutoudis M, Loros J, Dunlap J.C. 2008. Fully Codon-optimized luciferase Uncovers Novel Temperature Characteristics of the Neurospora Clock. **Eukaryotic Cell** 7:28-37.

d. Fuller, K.K., Chen, S., Loros, J.J., and Dunlap, J.C. 2015. Development of the CRISPR/Cas9 System for targeted Gene Disruptions in *Aspergillus fumigatus*. **Eukaryotic Cell** 14: 1073-1080.

222 career publications in total, 193 exclusive of edited books. Activity within the past decade is seen below.

 Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/jay.dunlap.1/bibliography/40810017/public/?sort=date&direction=ascending>

**D. Research Support**

## Ongoing Research Support

R35 GM118021 Dunlap (PI) 5/01/16-5/30/21

Genetic and Molecular Dissection of the *Neurospora*  Clock

 This effort has focused for the past 26 years on the molecular mechanism of eukaryotic circadian oscillators and the means through which they are reset by environmental cues.

Role: PI

U01 EB022546-01 Dunlap (co-PI) 8/1/16-7-31-20

 Multiscale Modeling of Circadian Rhythms

This cooperative project (one modeler and computational biologist and one experimentalist) seeks to develop and populate a mathematical model of the circadian system of a cell, using coupled reaction theory.