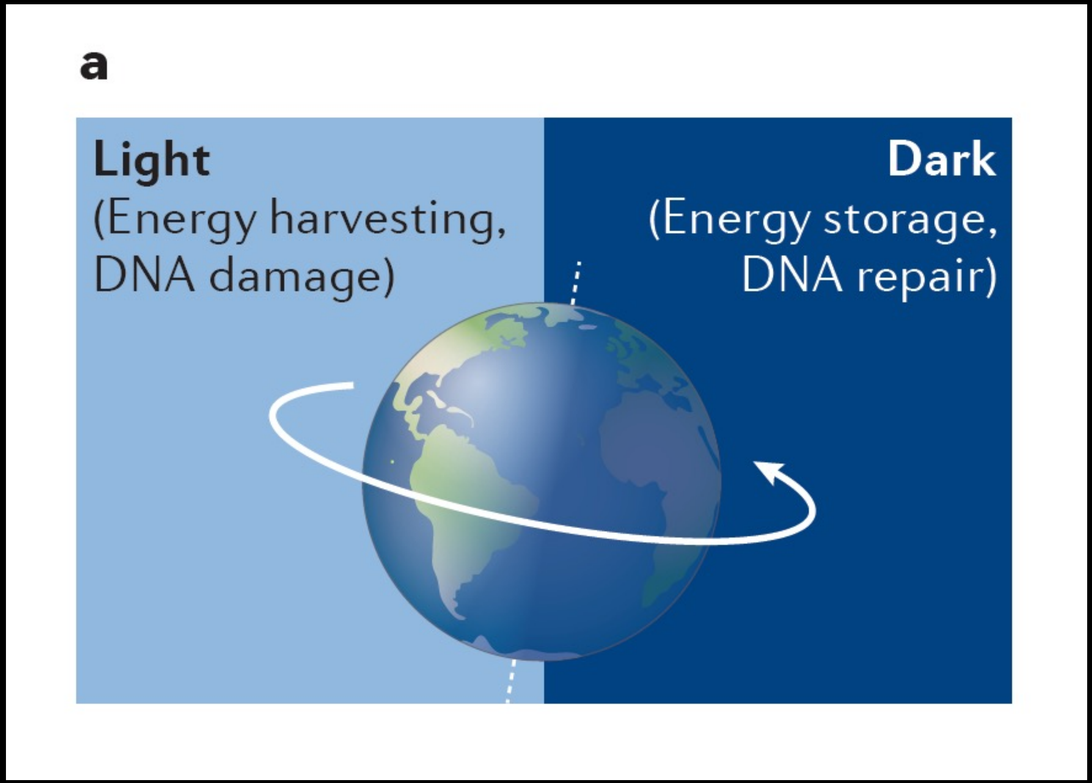
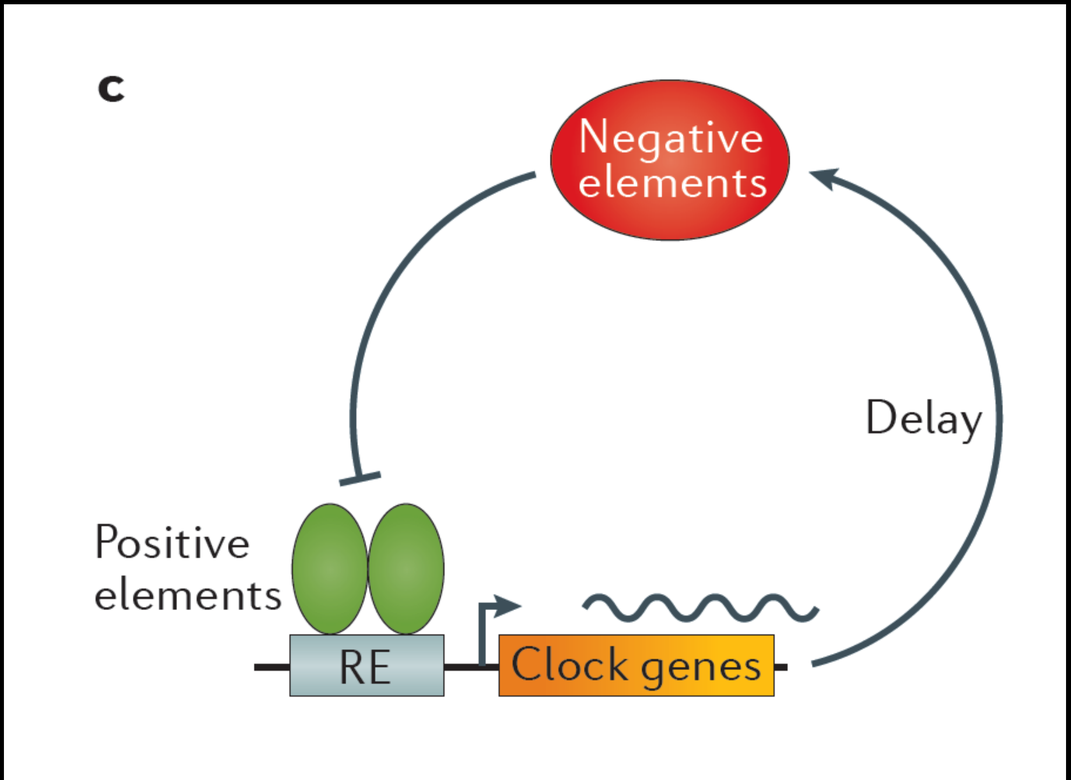
Circadian Clocks and Their Impact on Metabolism, Aging and Longevity

13th Symposium of the Bial Foundation
Behind and Beyond the Brain
The Mystery of Time
April 7, 2022

Joseph S. Takahashi
Department of Neuroscience
Howard Hughes Medical Institute
UT Southwestern Medical Center

Circadian clocks evolved to adapt to the 24-hour solar energetic cycle on earth





Takahashi 2017 *Nat Rev Genet* 18:164

ENU mutagenesis screen in mouse

Martha Vitaterna Northwestern University

Vitaterna et al. 1994 Science 264:719-725

Normal mouse activity

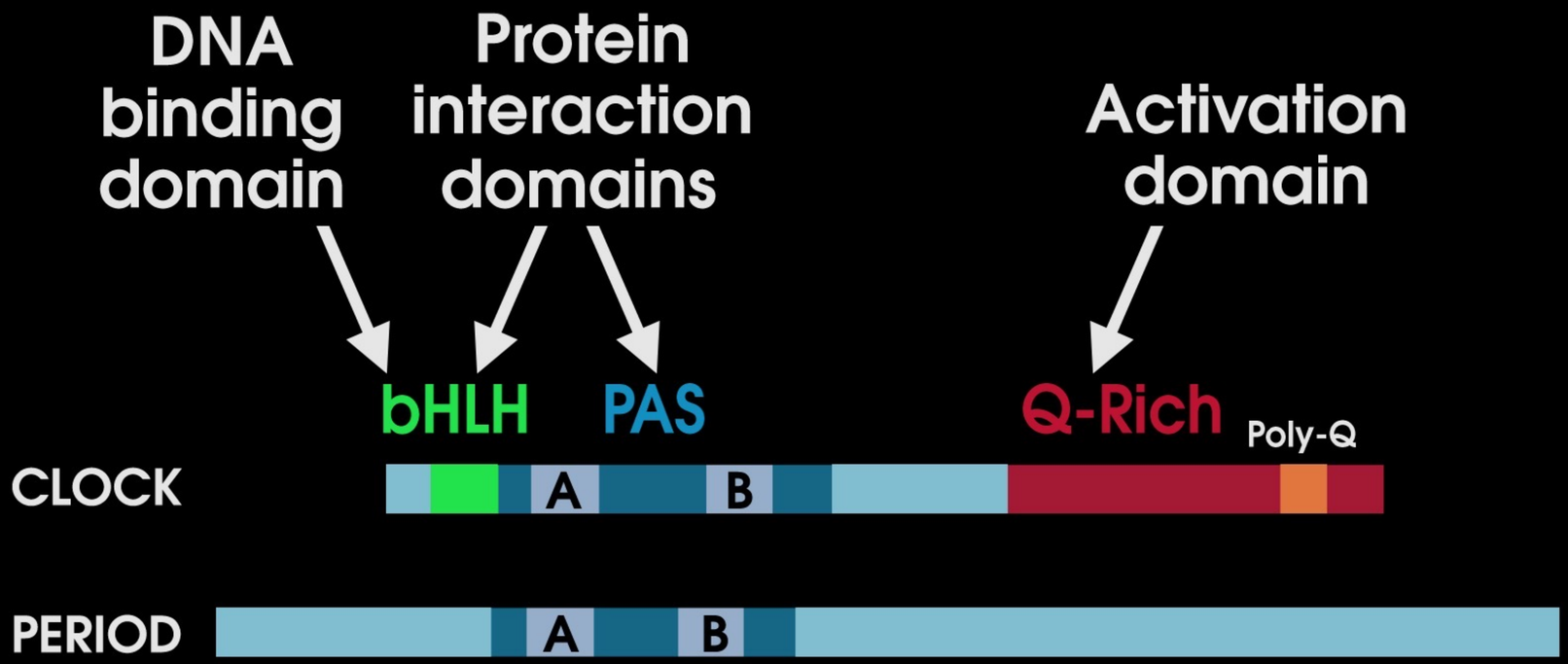
Clock mutant mouse

0 *24* *48*

Time of Day (hrs)

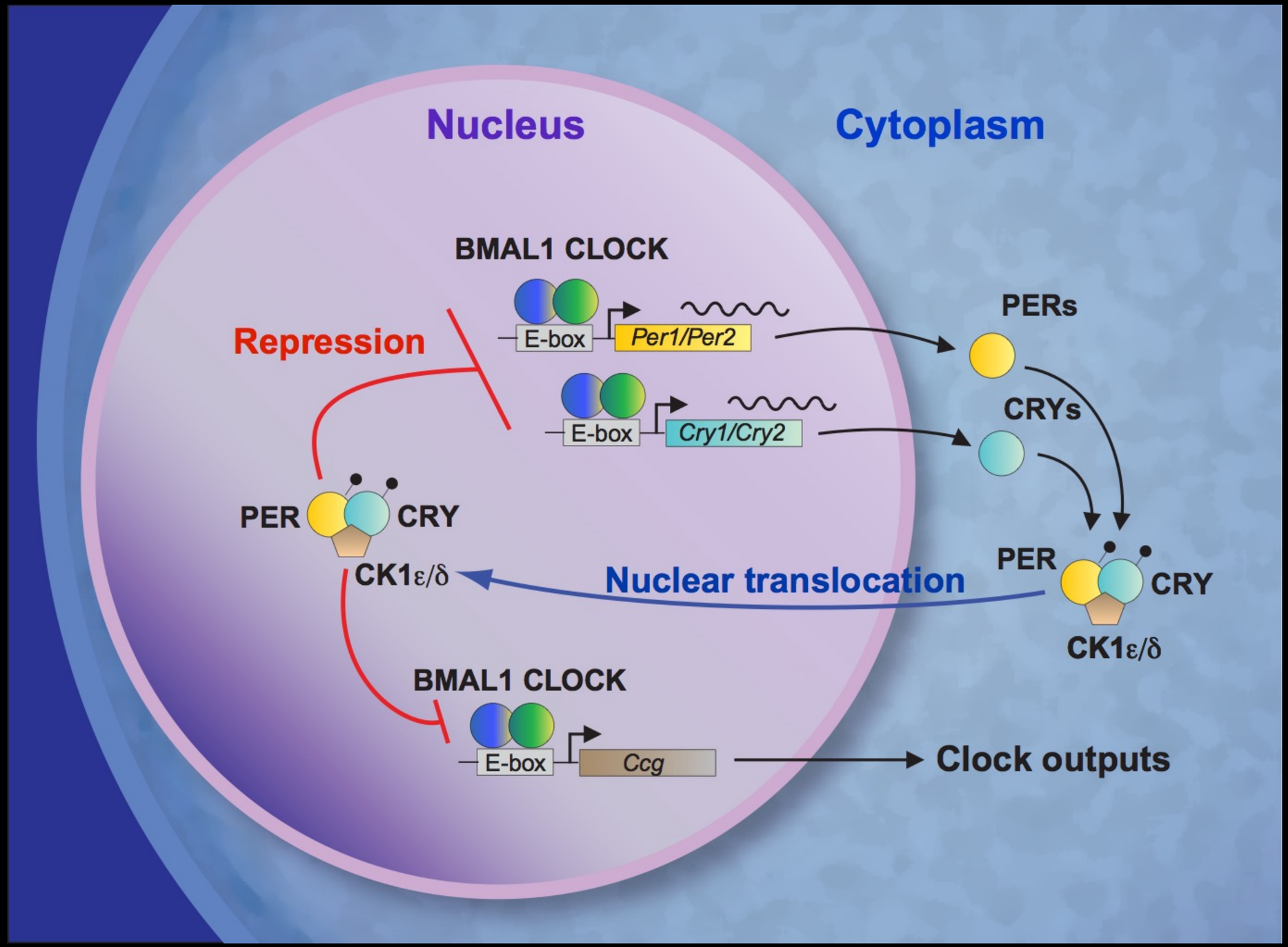
David King

CLOCK is a Basic Helix–Loop–Helix PAS Protein



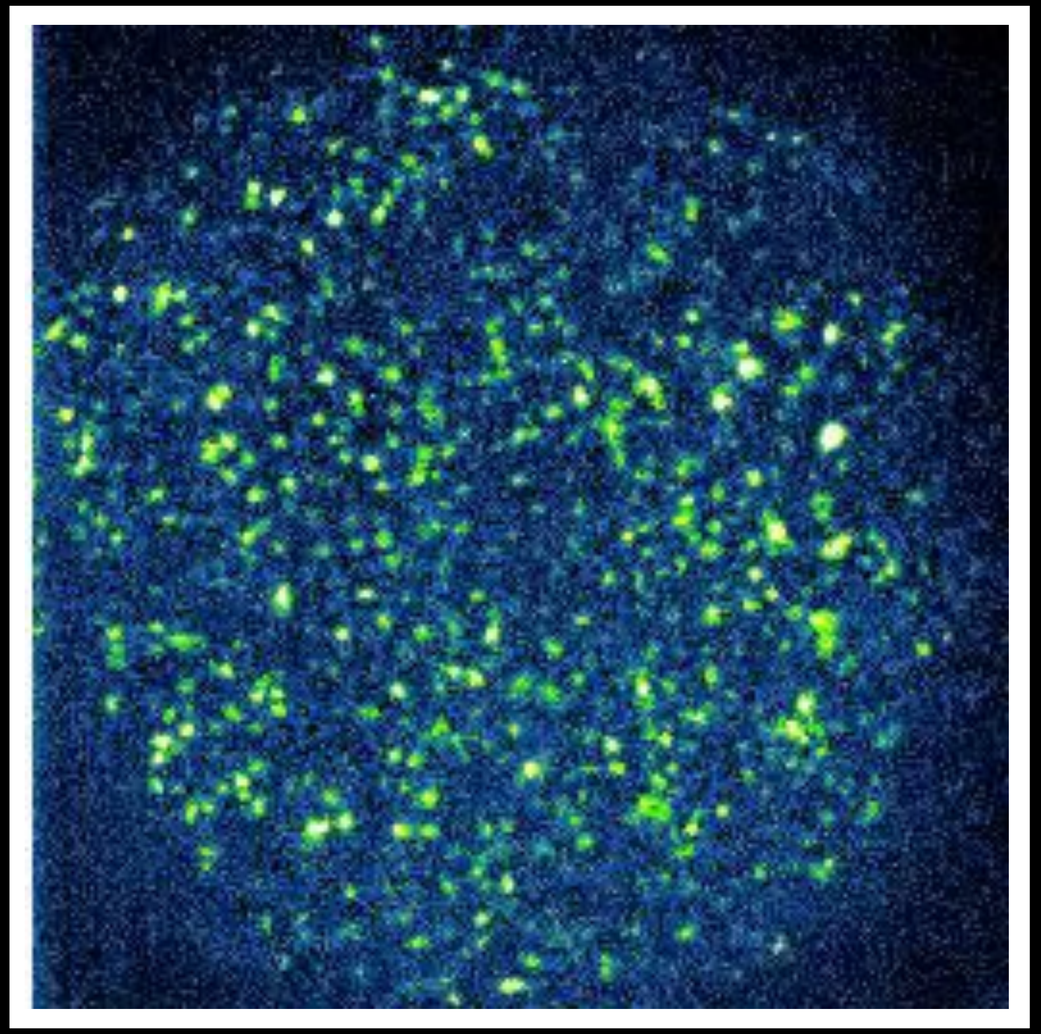
Marina Antoch

King et al. 1997 Cell 89:641-653; Antoch et al. 1997 Cell 89:655-667.
Gekakis et al. 1998 Science 280:1564.

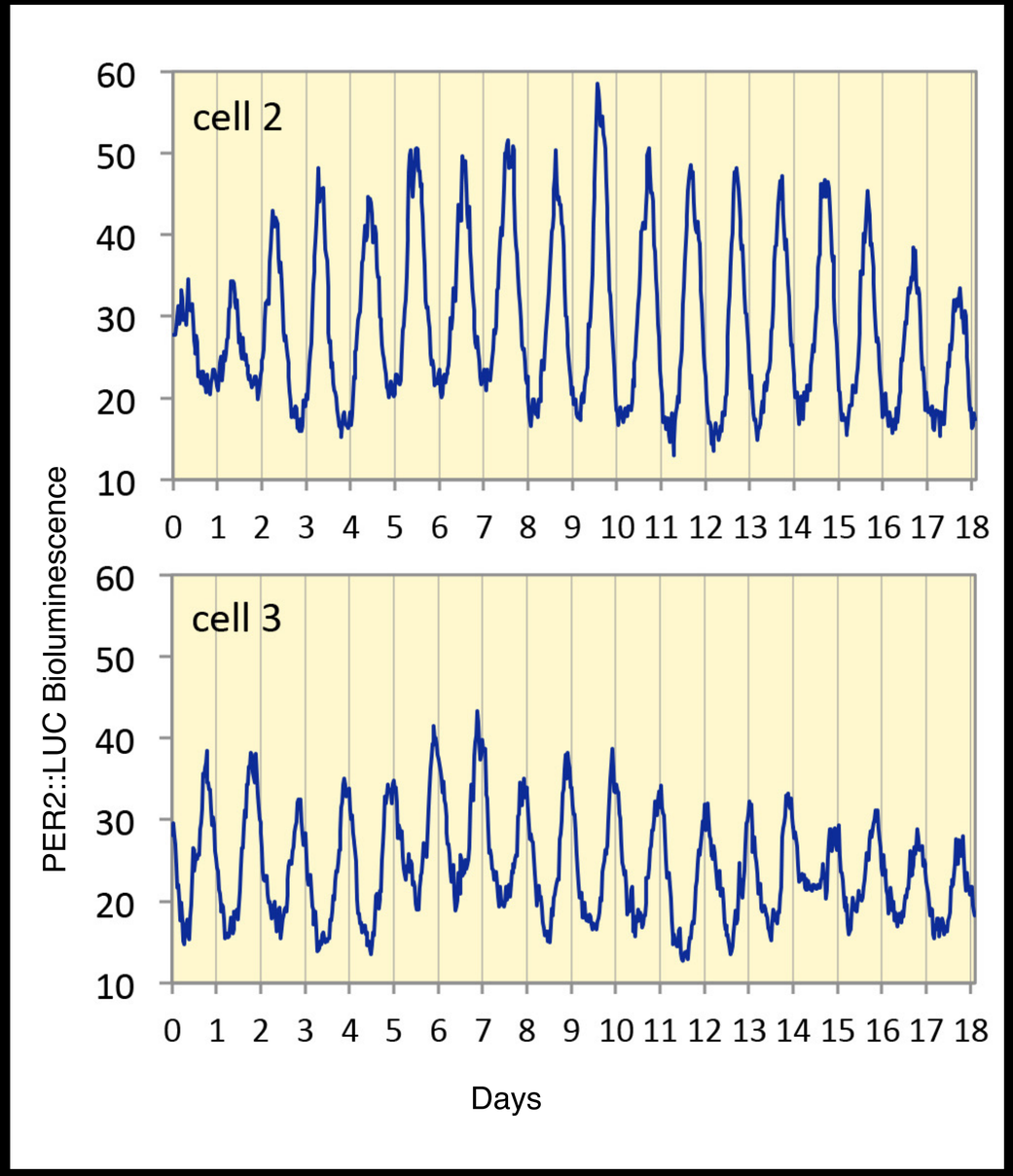


Circadian clock mechanism in mammals 1997-2000

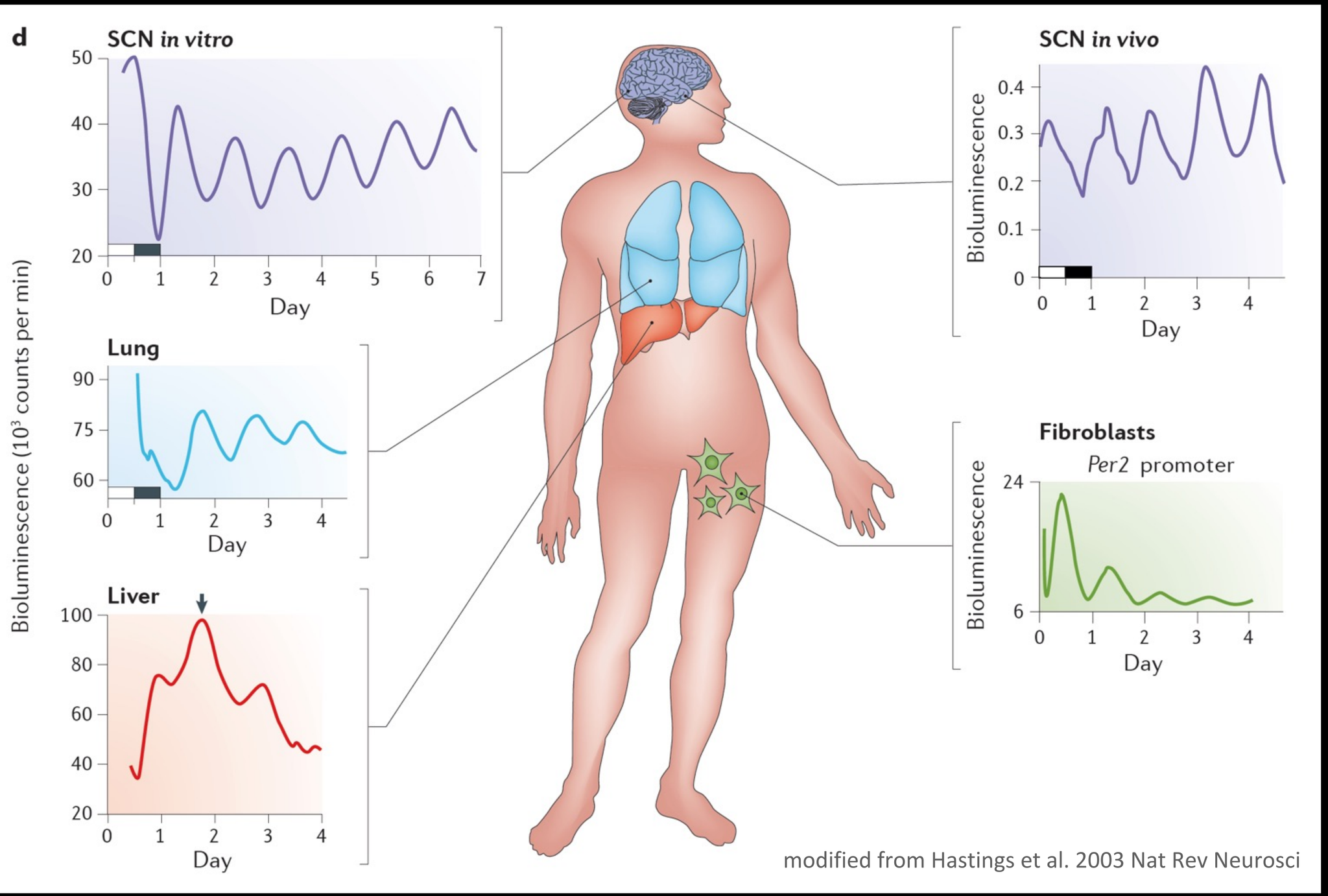
Single-cell rhythms in mouse fibroblasts



Yan Li 18-day time-lapse recording

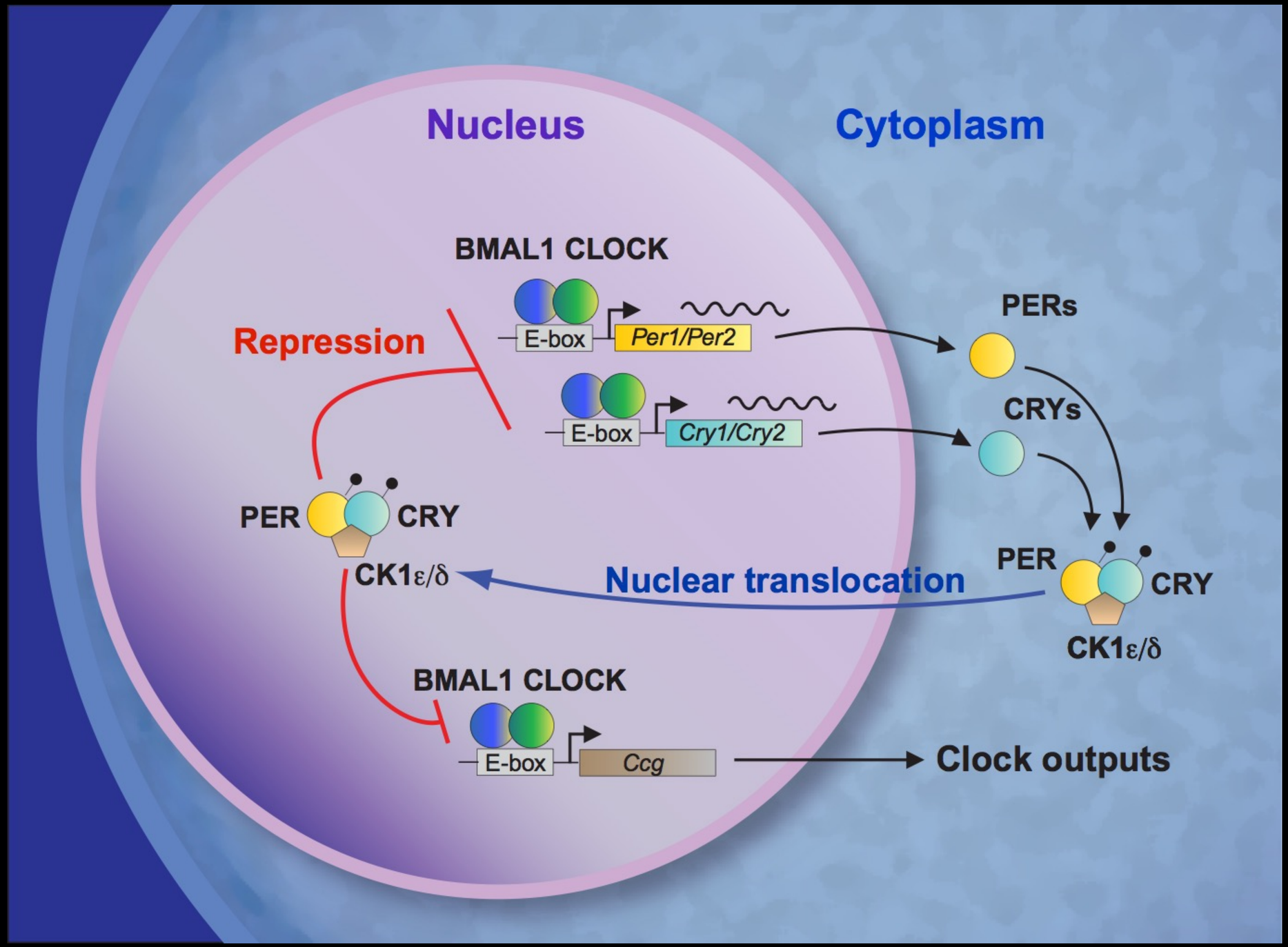


Li et al. 2020 PNAS 117:10350;
Li et al. 2020 eLife 9:e54186



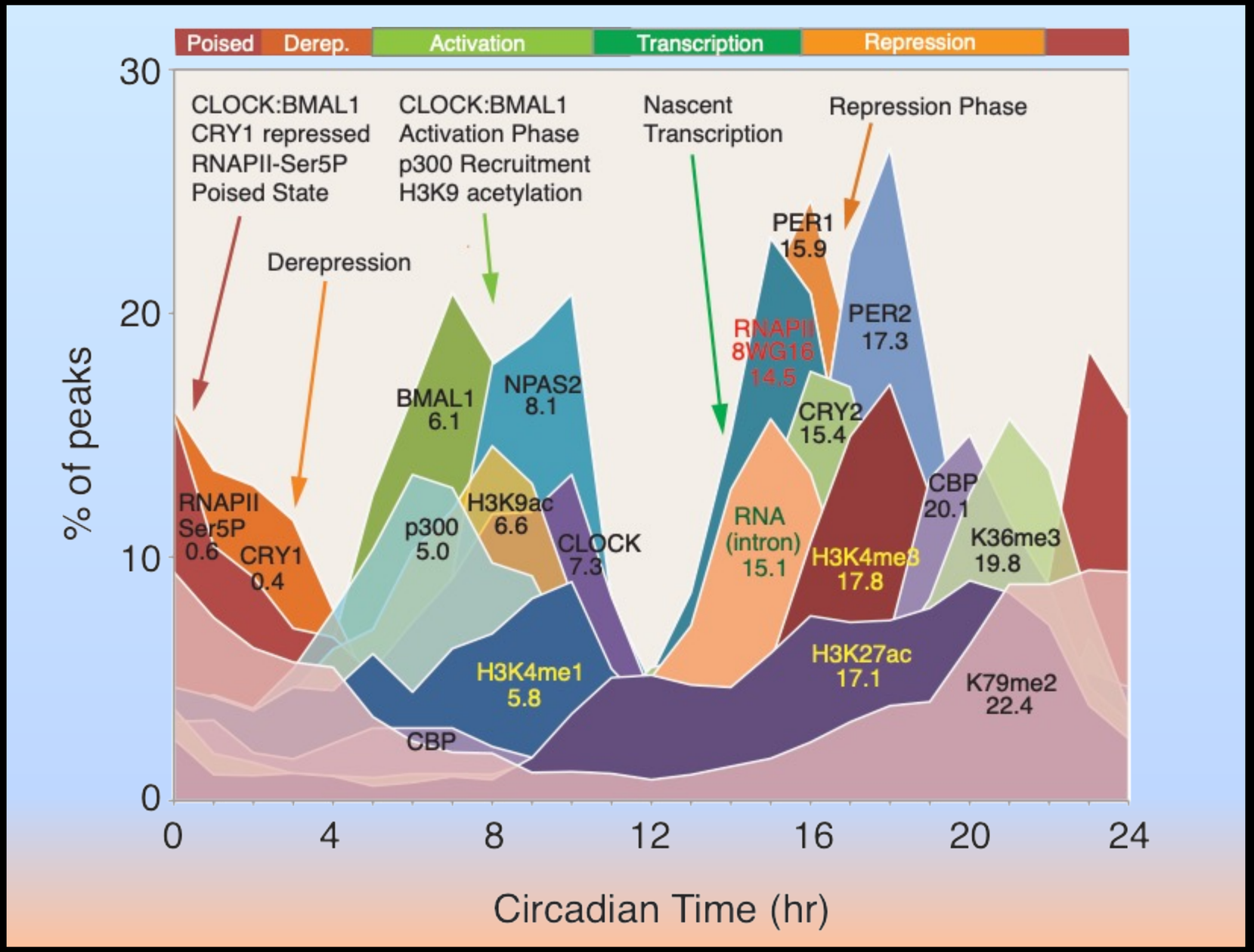
modified from Hastings et al. 2003 Nat Rev Neurosci

Clocks exist in all major organs, tissues and cells



Circadian clock mechanism in mammals

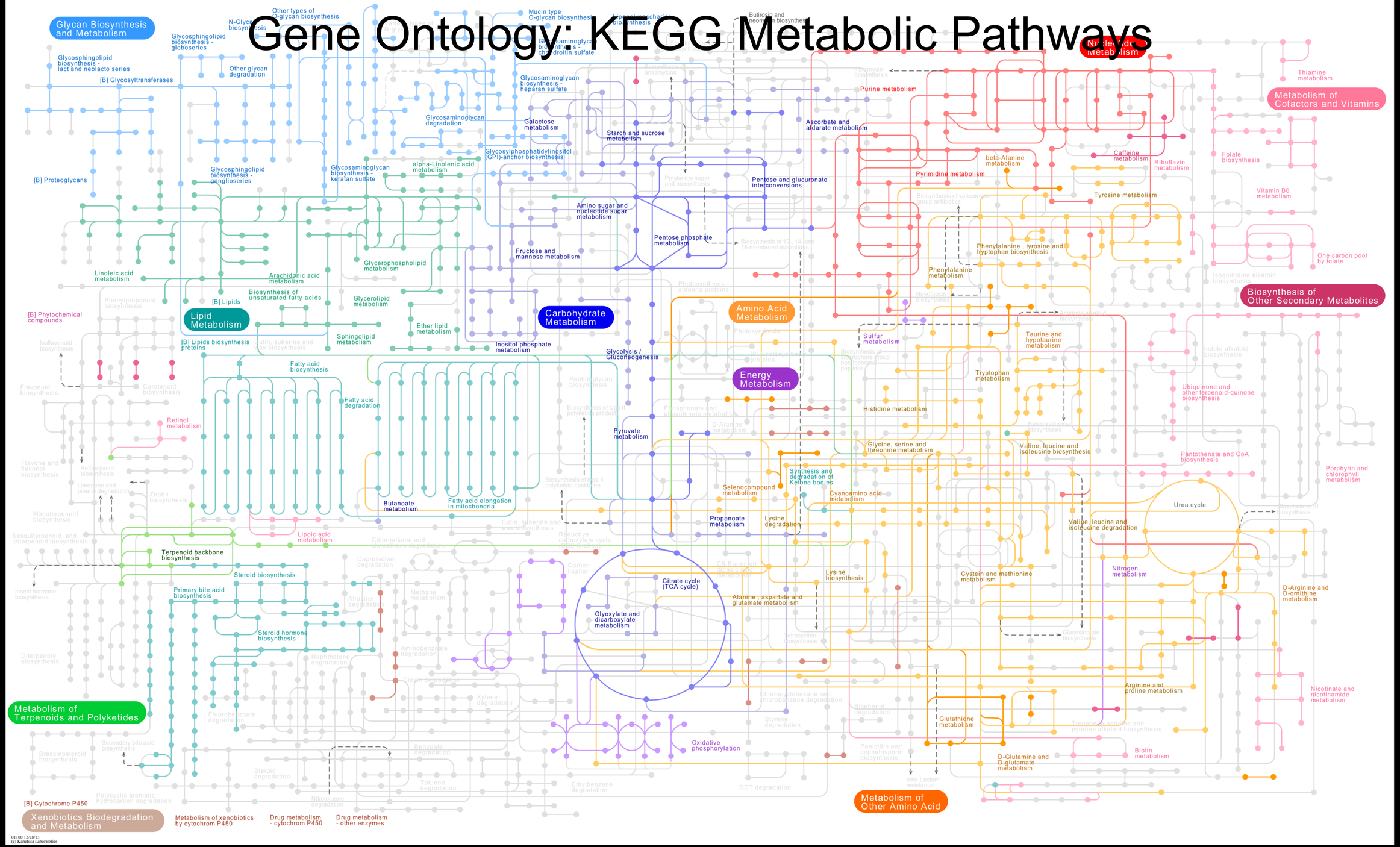
Circadian Transcriptional and Chromatin Landscape



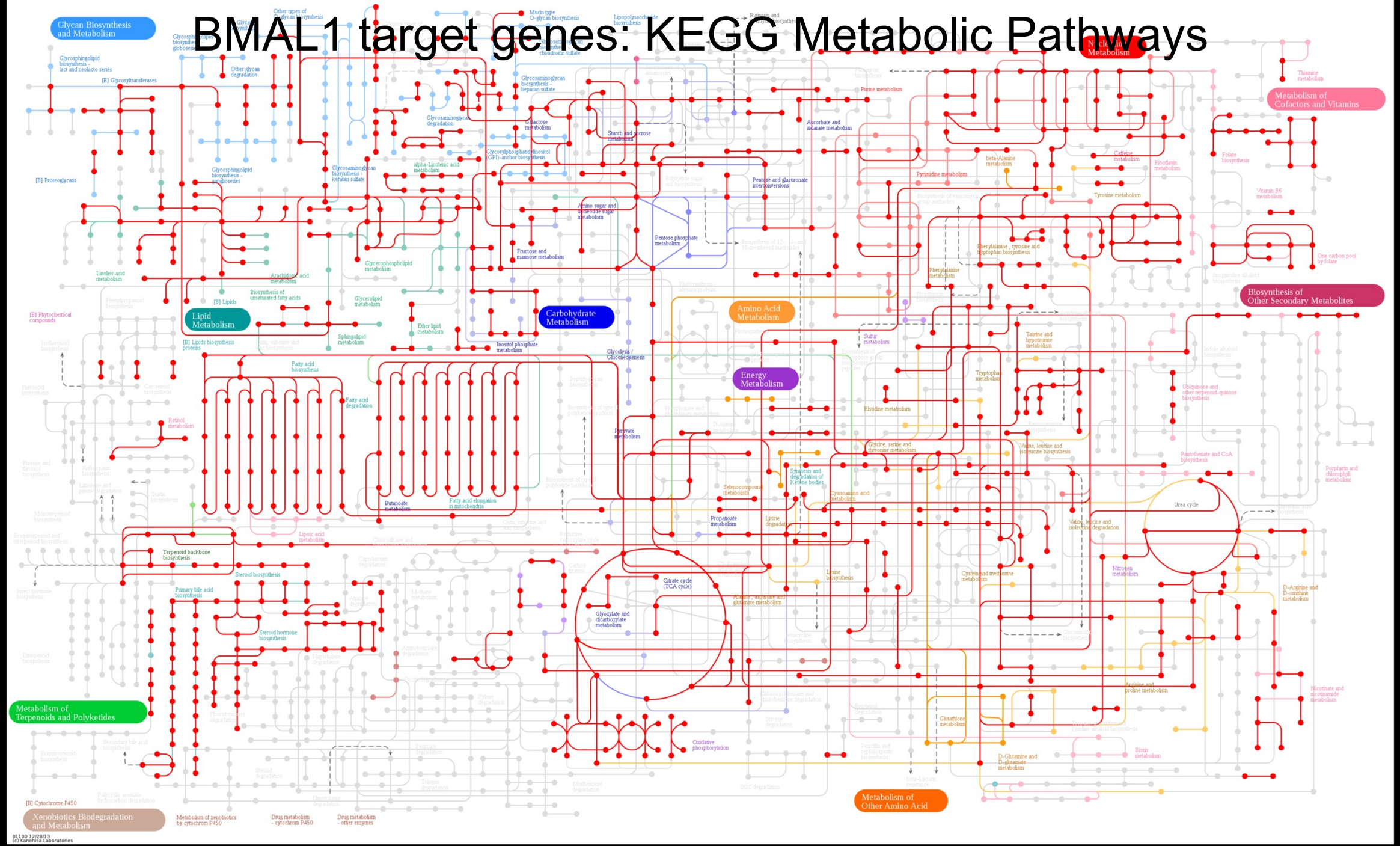
Nobuya Koike

Koike et al. *Science* 338:349 (2012)

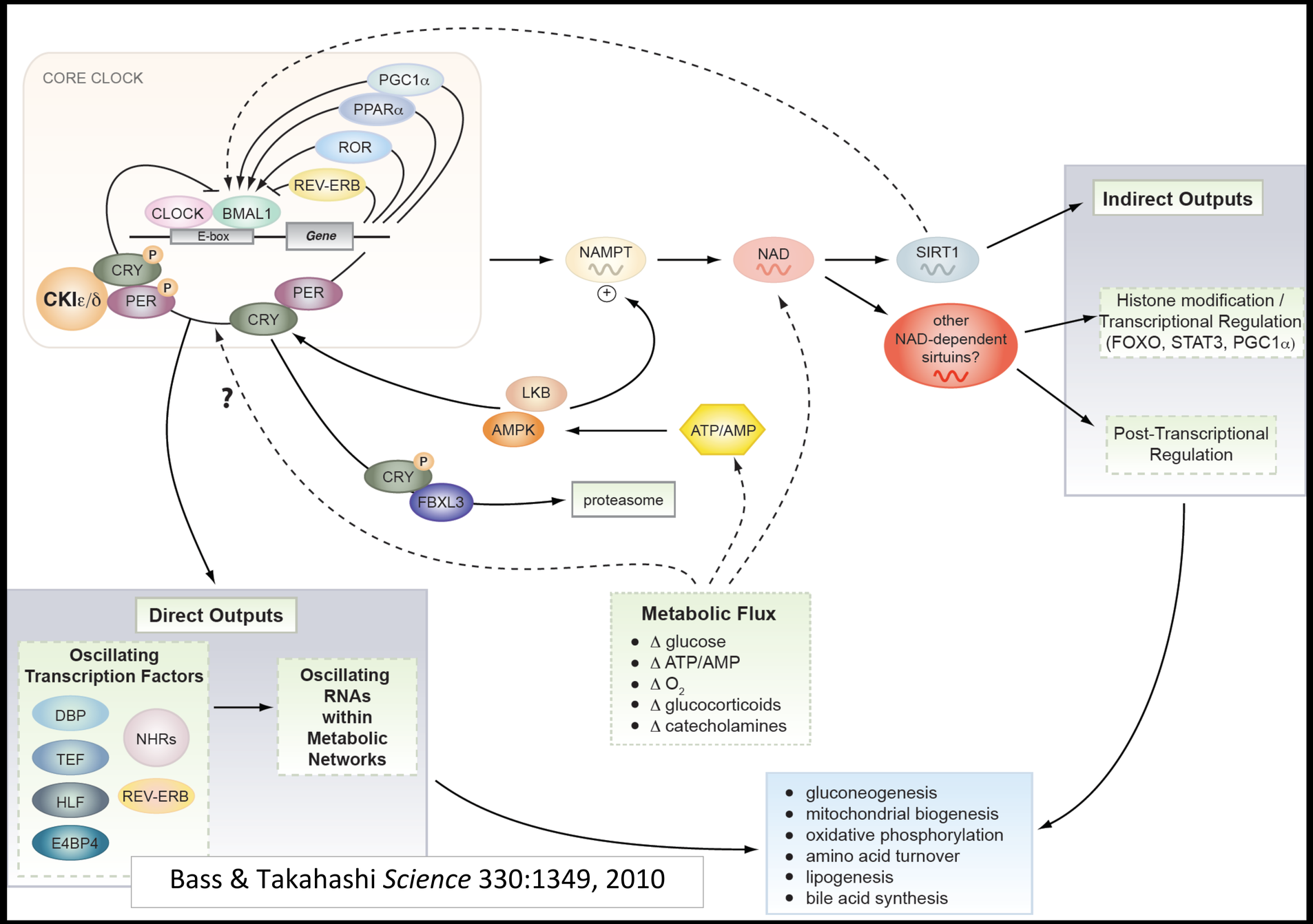
Gene Ontology: KEGG Metabolic Pathways



BMAL1 target genes: KEGG Metabolic Pathways



Time vs. calories



Bass & Takahashi *Science* 330:1349, 2010

Circadian clocks and metabolism are intimately and reciprocally connected at the molecular level

nature publishing group

SHORT COMMUNICATIONS
INTEGRATIVE PHYSIOLOGY

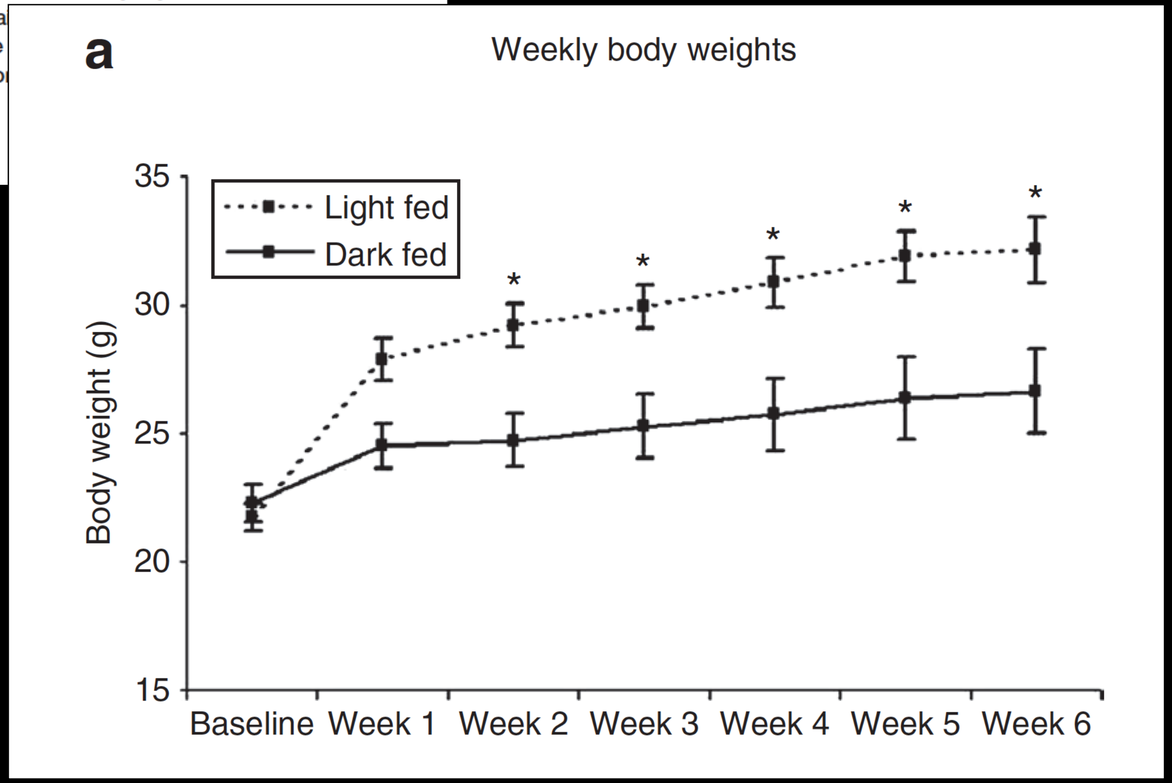
Circadian Timing of Food Intake Contributes to Weight Gain

Deanna M. Arble[1], Joseph Bass[1,2], Aaron D. Laposky[1], Martha H. Vitaterna[1] and Fred W. Turek[1]

Studies of body weight regulation have focused almost entirely on caloric intake and energy expenditure. However, a number of recent studies in animals linking energy regulation and the circadian clock at the molecular, physiological, and behavioral levels raise the possibility that the timing of food intake itself may play a significant role in weight gain. The present study focused on the role of the circadian phase of food consumption in weight gain. We provide evidence that nocturnal mice fed a high-fat diet only during the 12-h light phase ga
mice fed only during the 12-h dark phase. A better understanding of the role of the
could have important implications for developing new therapeutic strategies for co
facing the human population today.

Obesity (2009) doi:10.1038/oby.2009.264

Fred Turek
Northwestern University



Arble et al. Obesity 17:2100, 2009

Time-restricted feeding prevents effects of high-fat diet on metabolism

Satchin Panda Salk

Cell PRESS

Cell Metabolism
Article

Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet

Megumi Hatori,[1,4] Christopher Vollmers,[1,4] Amir Zarrinpar,[1,2,4] Luciano DiTacchio,[1,4] Eric A. Bushong,[3] Shubhroz Gill,[1] Mathias Leblanc,[1] Amandine Chaix,[1] Matthew Joens,[1] James A.J. Fitzpatrick,[1] Mark H. Ellisman,[3] and Satchidananda Panda[1,*]

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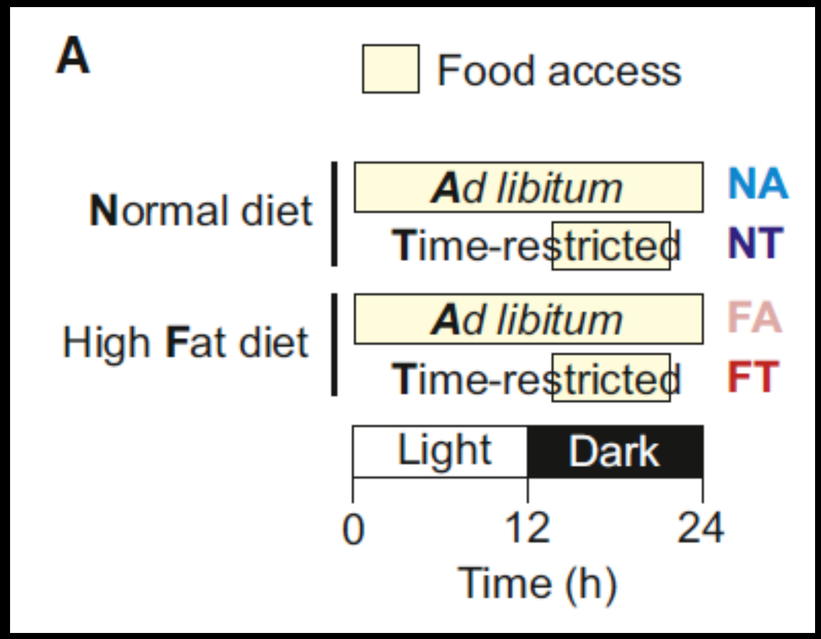
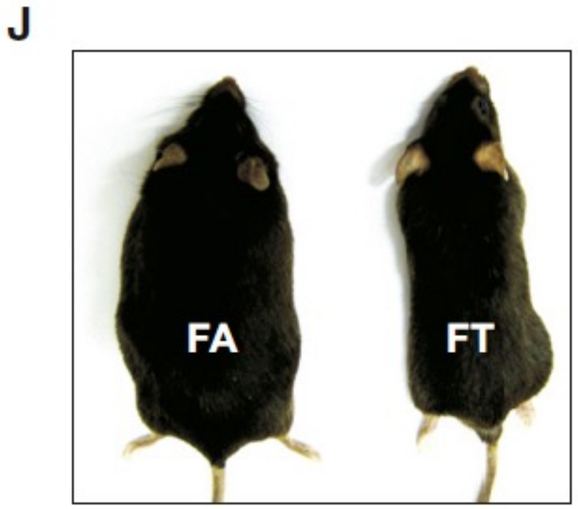
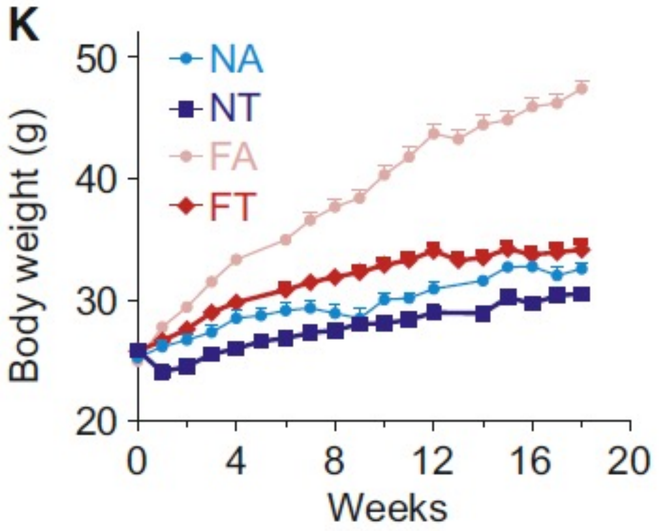
[2]Department of Gastroenterology, University of California, San Diego, La Jolla, CA 92037, USA
[3]National Center for Microscopy and Imaging Research, University of California, San Diego, La Jolla, CA 92093, USA
[4]These authors contributed equally to this work
*Correspondence: satchin@salk.edu
DOI 10.1016/j.cmet.2012.04.019







Hatori et al. Cell Metab 15:848, 2012

Mouse

Cell Metabolism
Article

Time-Restricted Feeding Is a Preventative and Therapeutic Intervention against Diverse Nutritional Challenges

Amandine Chaix,[1] Amir Zarrinpar,[1,2] Phuong Miu,[1] and Satchidananda Panda[1,*]

Cell Metabolism
Article

Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock

Amandine Chaix,[1] Terry Lin,[1] Hiep D. Le,[1] Max W. Chang,[2] and Satchidananda Panda[1,3,*]

Cell Metabolism
Short Article

Daily Fasting Improves Health and Survival in Male Mice Independent of Diet Composition and Calories

Sarah J. Mitchell,[1,8] Michel Bernier,[1] Julie A. Mattison,[1] Miguel A. Aon,[1,2] Tamzin A. Kaiser,[1] R. Michael Anson,[1,3] Yuji Ikeno,[4] Rozalyn M. Anderson,[5,6] Donald K. Ingram,[7] and Rafael de Cabo[1,9,10,*]

Cell Metabolism
Clinical and Translational Report

Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes

Elizabeth F. Sutton,[1] Robbie Beyl,[1] Kate S. Early,[2] William T. Cefalu,[1,3] Eric Ravussin,[1] and Courtney M. Peterson[1,4,5,*]

Cell Metabolism
Clinical and Translational Report

Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging

Leanne M. Redman,[1,4,*] Steven R. Smith,[2] Jeffrey H. Burton,[1] Corby K. Martin,[1] Dora Il'yasova,[3] and Eric Ravussin[1]

Cell Metabolism
Report Clinical

Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome

Michael J. Wilkinson,[1,3] Emily N.C. Manoogian,[2,3] Adena Zadourian,[1] Hannah Lo,[1] Savannah Fakhouri,[2] Azarin Shoghi,[2] Xinran Wang,[2] Jason G. Fleischer,[2] Saket Navlakha,[2] Satchidananda Panda,[2,4,*] and Pam R. Taub[1,*]

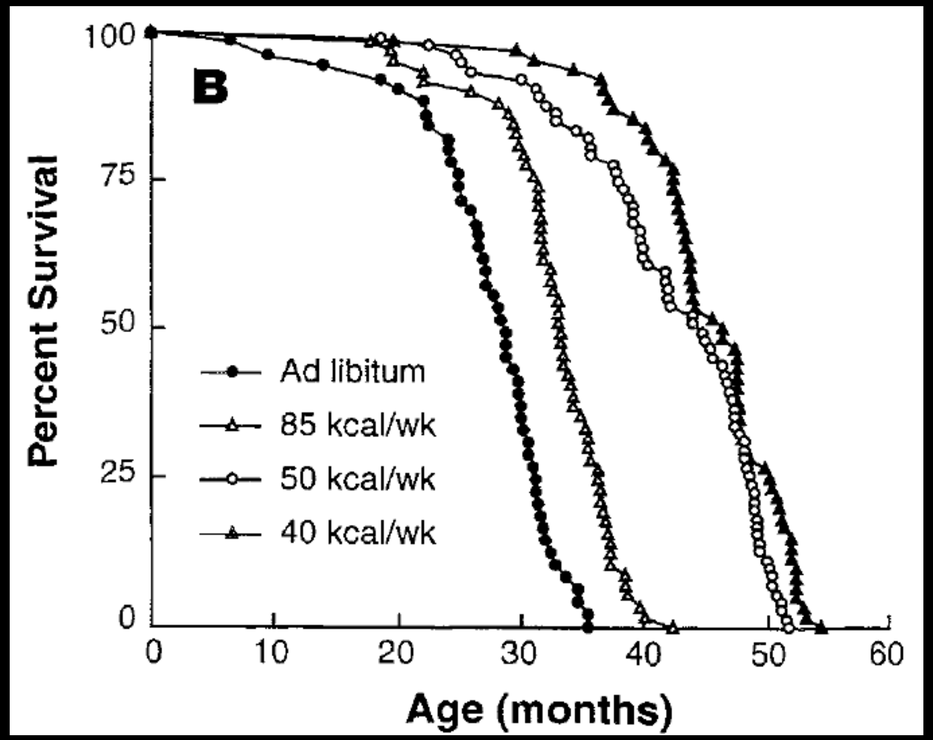
Human

Caloric restriction paradigms often introduce temporal restriction

The Retardation of Aging in Mice by Dietary Restriction: Longevity, Cancer, Immunity and Lifetime Energy Intake[1]

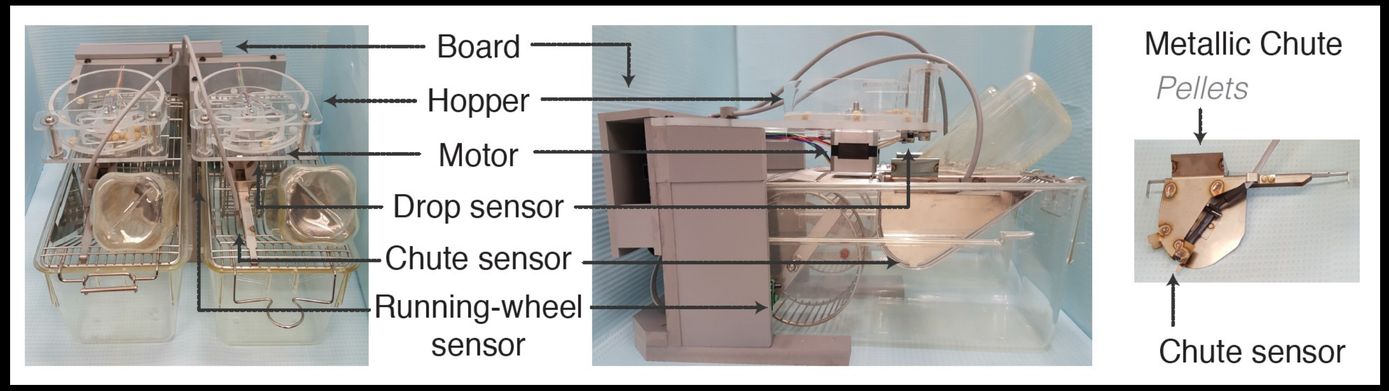
RICHARD WEINDRUCH, ROY L. WALFORD, SUZANNE FLIGIEL[2] AND DONALD GUTHRIE*

*Department of Pathology, University of California, Los Angeles, CA 90024 and *Mental Retardation Research Center, University of California, Los Angeles, CA 90024*

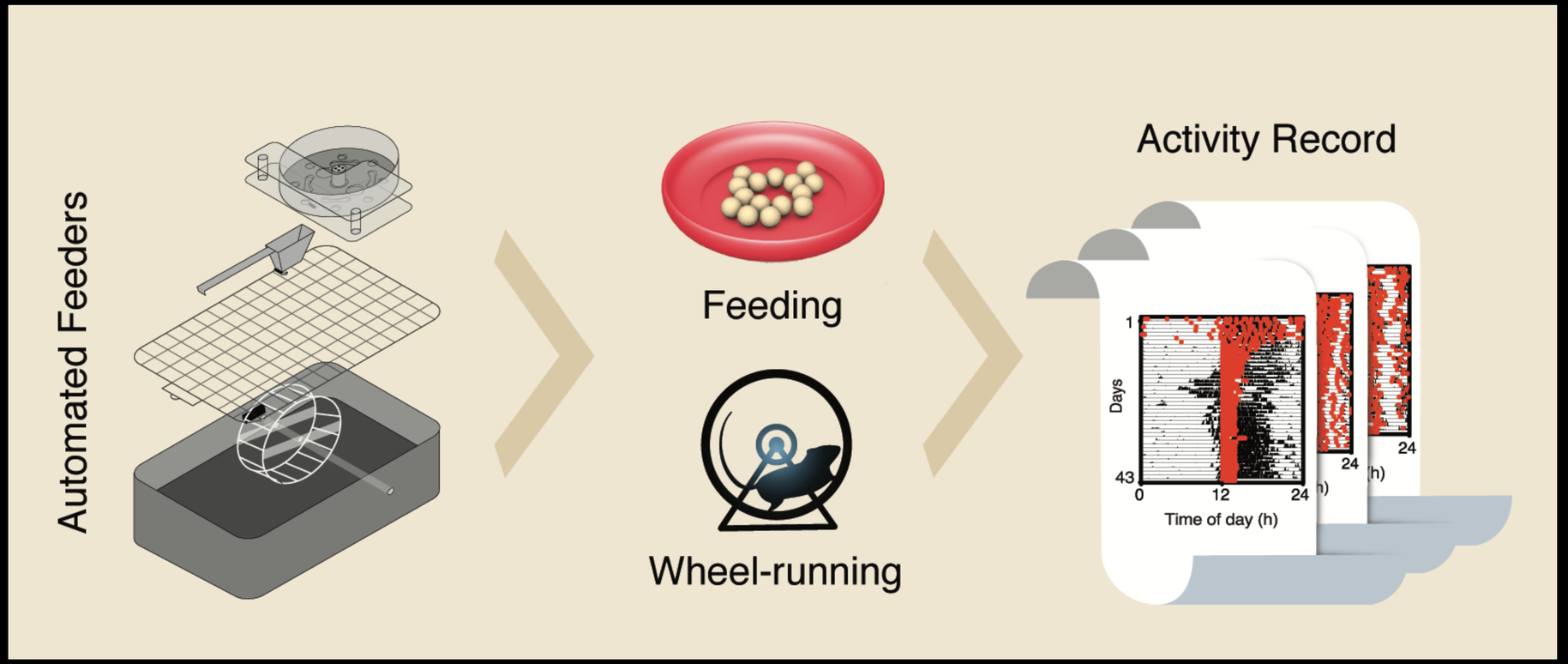


Each mouse was fed four feedings (3.0–3.2 g) per week (one daily feeding on Monday and Wednesday mornings; a double feeding on Friday morning).

Weindruch et al. J Nutr 1116:641, 1986; NEJM 337:986, 1997

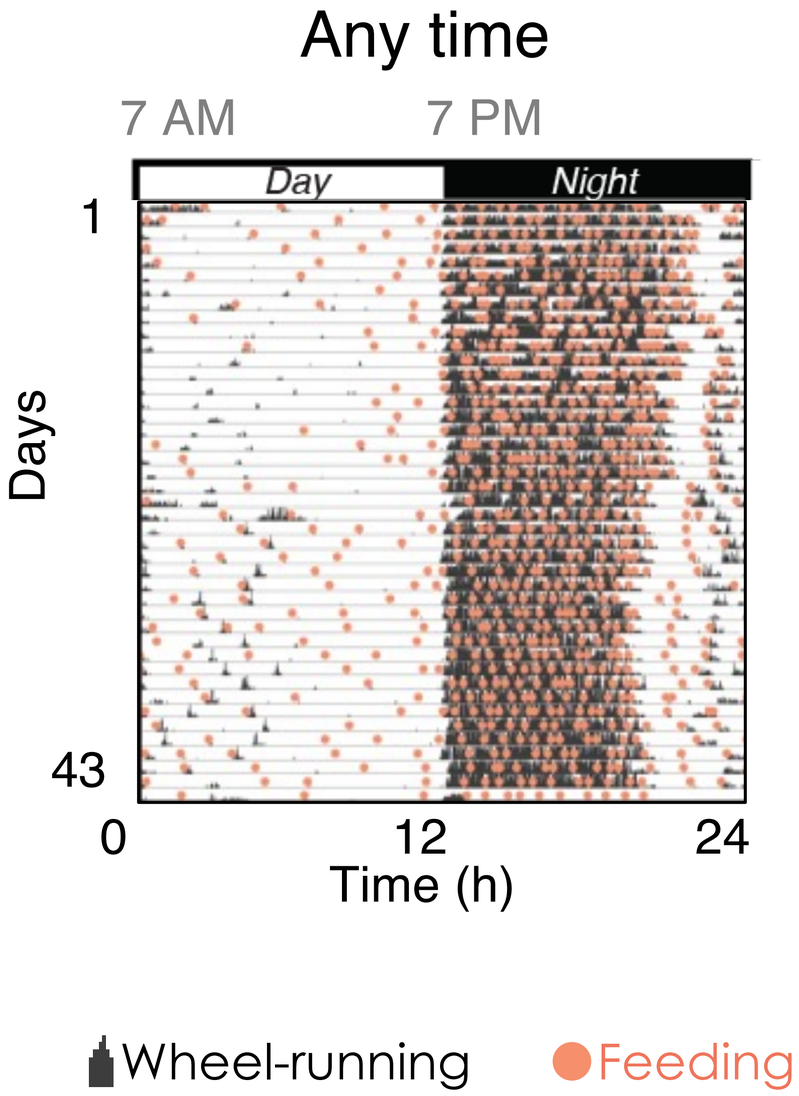


Victoria Acosta-Rodriguez
UT Southwestern

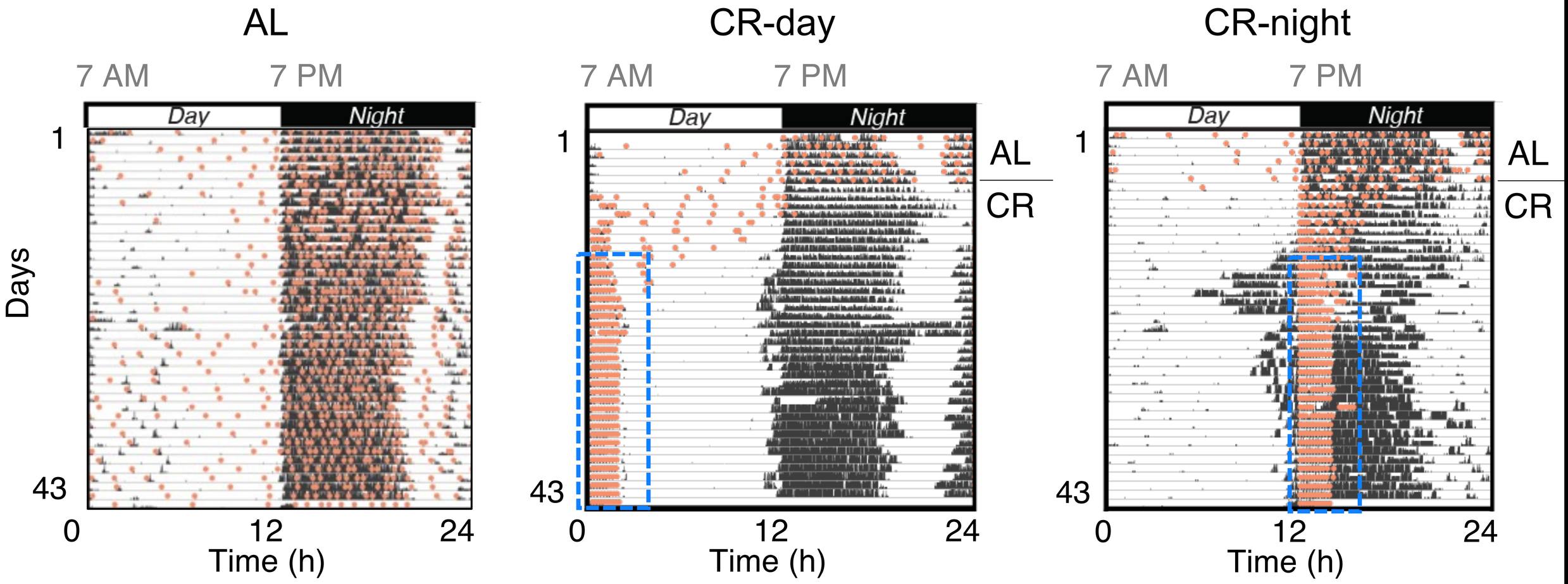


Acosta-Rodriguez et al. Cell Metab 26:267, 2017

Feeding and locomotor activity rhythms under Ad lib feeding



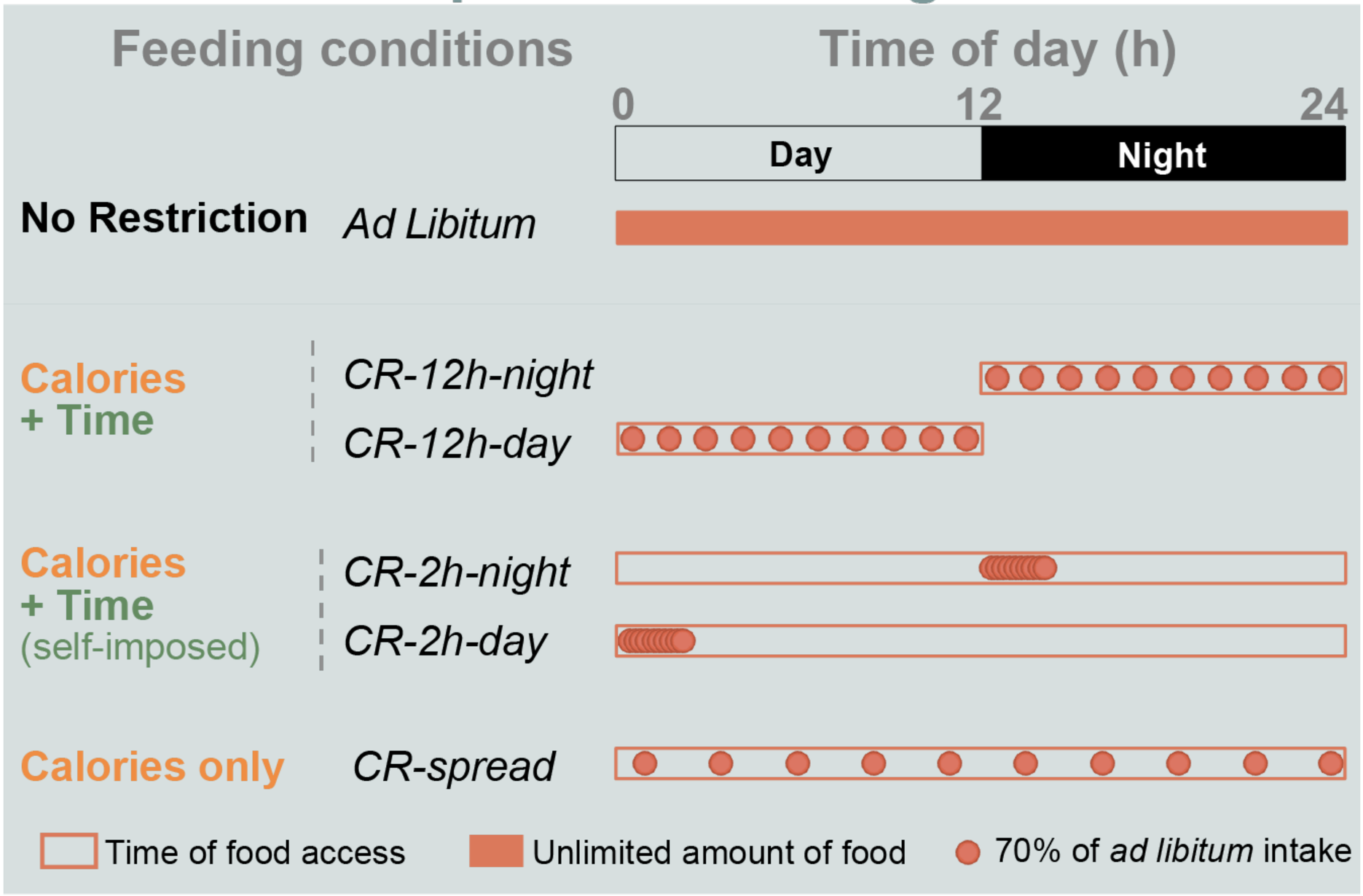
Calorically restricted mice consolidate their intake to a 2h window



Classic "CR" protocols

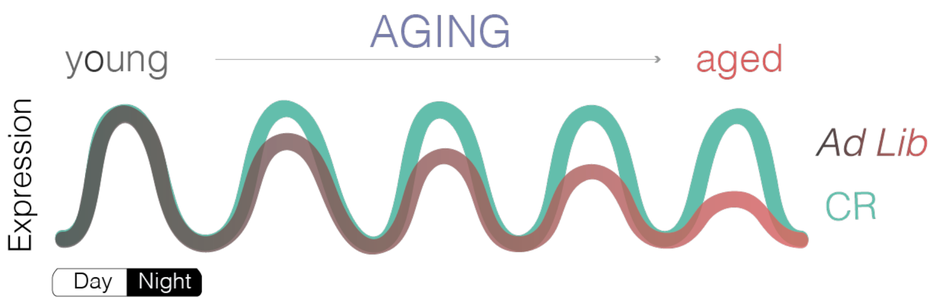
- ↓ Calories
- ↓ Feeding Time (onset)
- ↑ Feeding/Fasting Duration

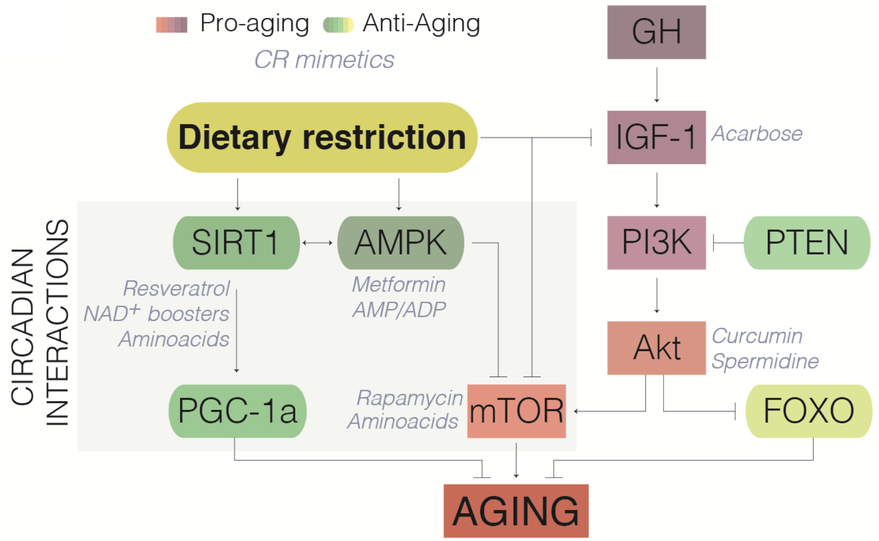
Experimental design

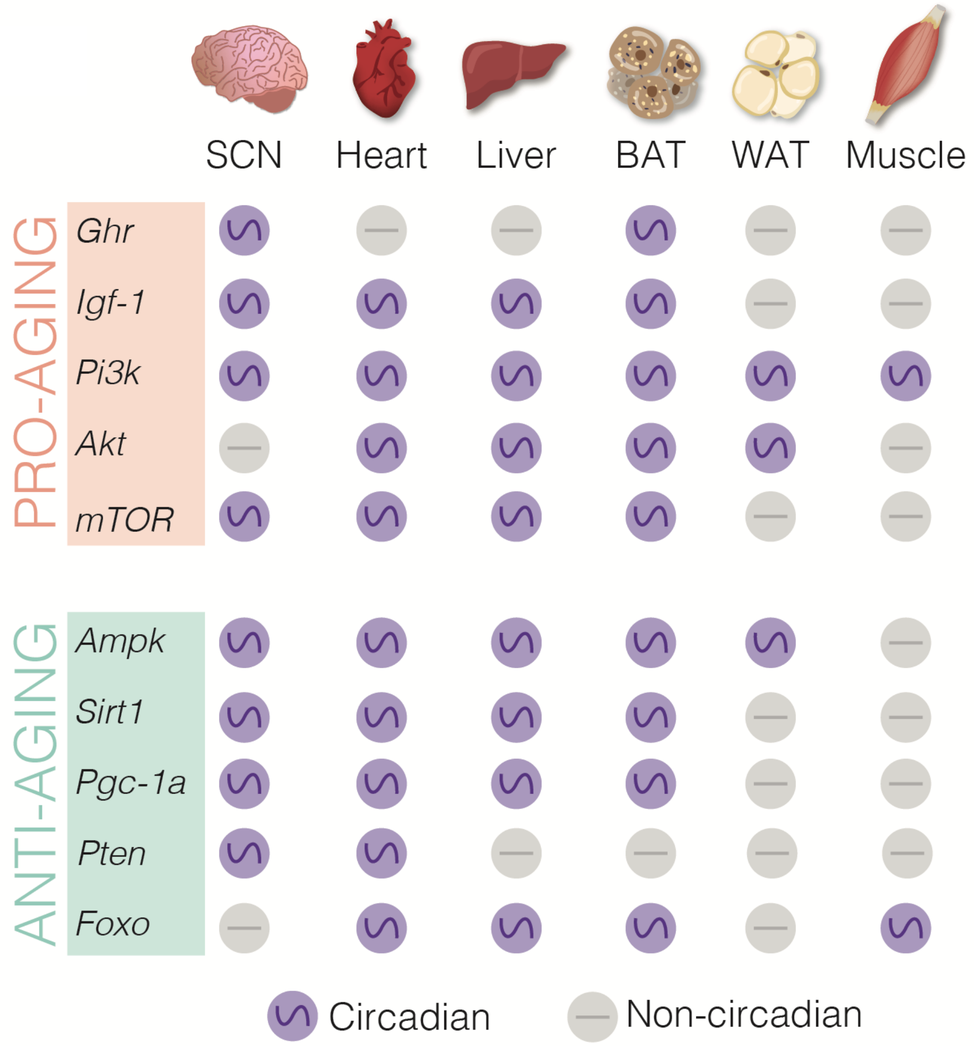


Sorry, the CR and longevity results
are embargoed by Science magazine
until publication. The paper is in press.

Longevity pathways are under circadian regulation

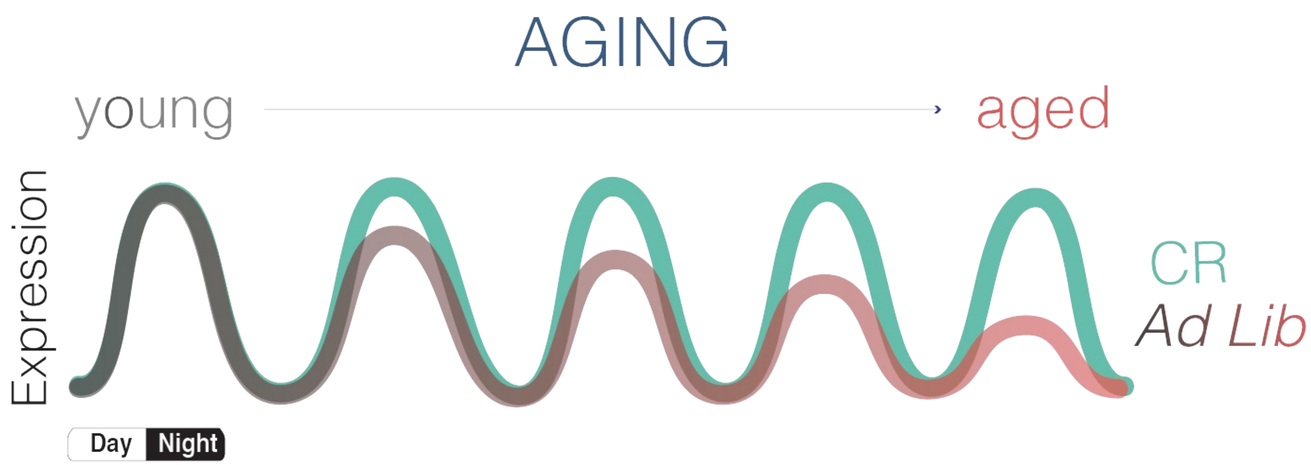


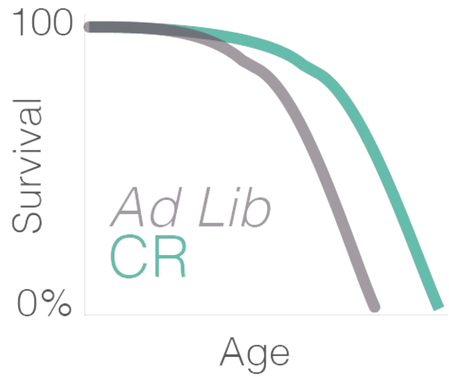




Acosta-Rodríguez V. (*Nat Comm* 2021) & from CircaDB – Hogenesch lab

RATIONALE





Hypothesis: Interventions that improve circadian rhythms promote health, increase lifespan and delay the aging process.

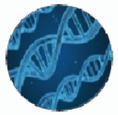
Test whether enhancement of circadian gene expression extend health & lifespan, using:

AIM

1. Time-restricted feeding

Does TRF improve health and lifespan?

2. Genetic intervention



Can manipulation of the circadian gene "*Clock*" extend lifespan?

3. Pharmacological intervention

Uncover small molecules that regulate CLOCK/BMAL1 activity

Text

Acknowledgments

Victoria Acosta-Rodriguez, PhD
Carla Green, PhD

UT Southwestern

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Mariko Izumo, PhD
Pin Xu, PhD
Samantha liams, PhD
Shuzhang Yang, PhD
Nathan Skinner, PhD
Isara Laothamatas, PhD
Yoga Chelliahm MS
Emil Rasmussen, PhD

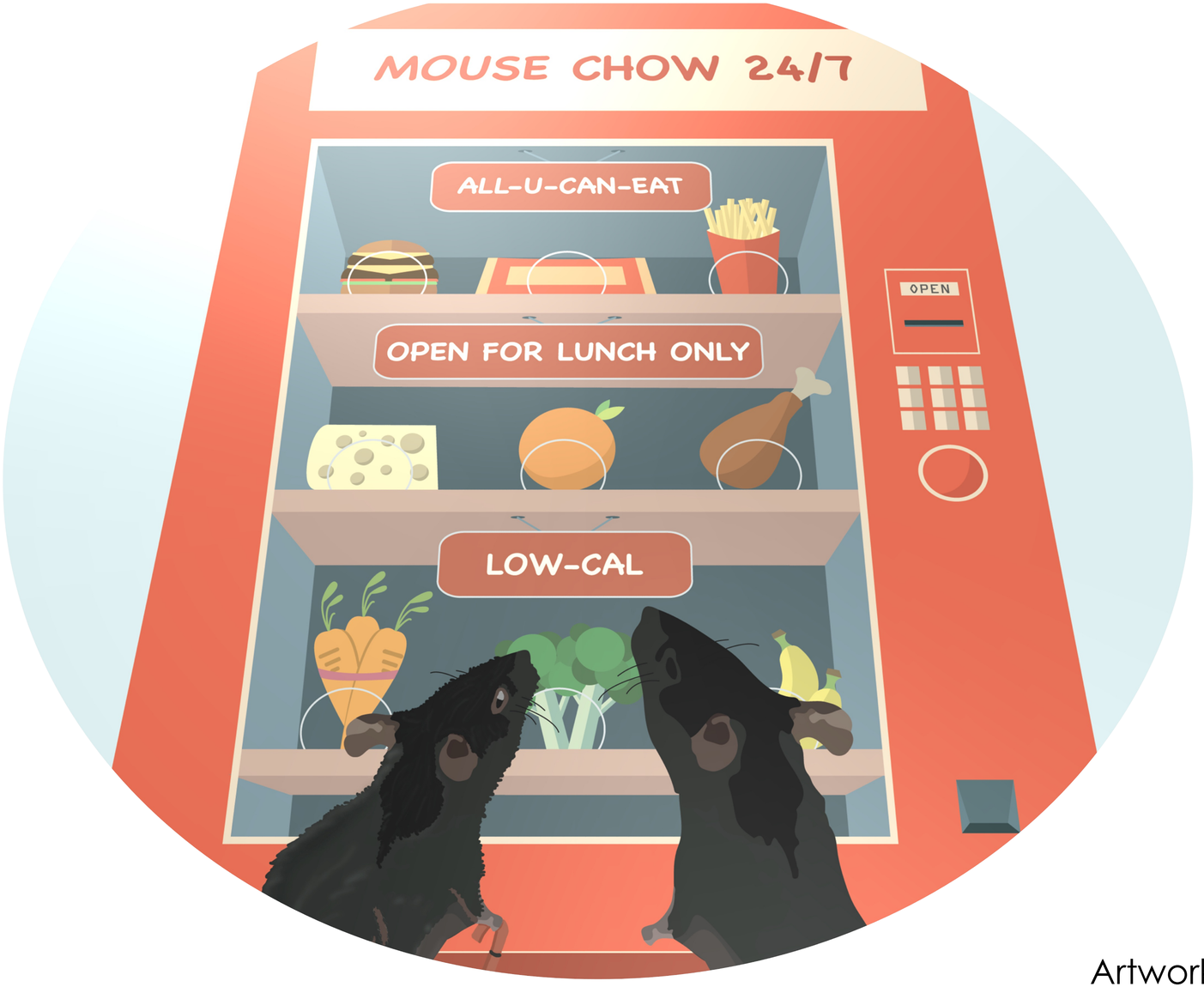
Automated Feeder System

David Ferster (*Actimetrics*)
Mike Wellems (*Phenome Technologies)*

UT Southwestern Medical Center

hhmi

NIH



Artwork
Fernando Augusto