From Bench to Bedtime: Entraining Policy to Science

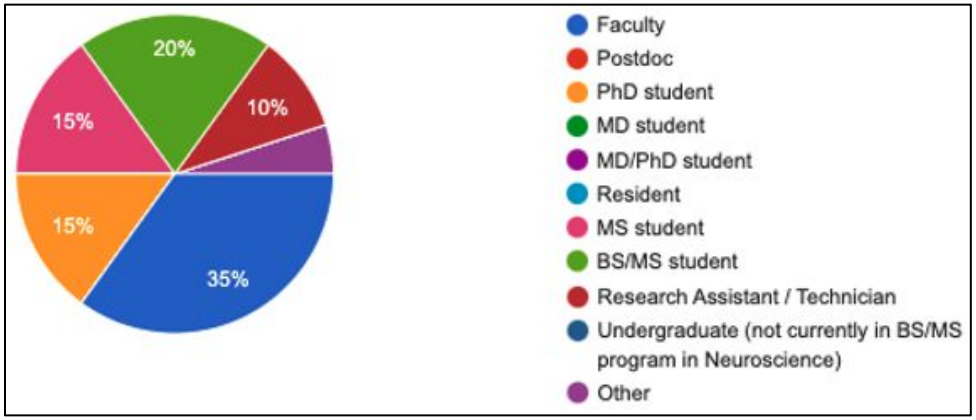
Day 1

Instructors: Ben Finander, Lauren Miner, Jackie Lin, Rachel Swope

We are the initial cohort of MAHPING Pedagogy Fellows!

- MAHPING: The Morehouse and Harvard Program in Neuroscience Growth
- Pedagogy Fellows: Seven graduate students across both institutions come together to learn inclusive teaching strategies and co-teach a course at both Harvard and Morehouse
- We chose to design and teach a course on applying circadian biology to policy decisions
- Website: **bit.ly/mahping**

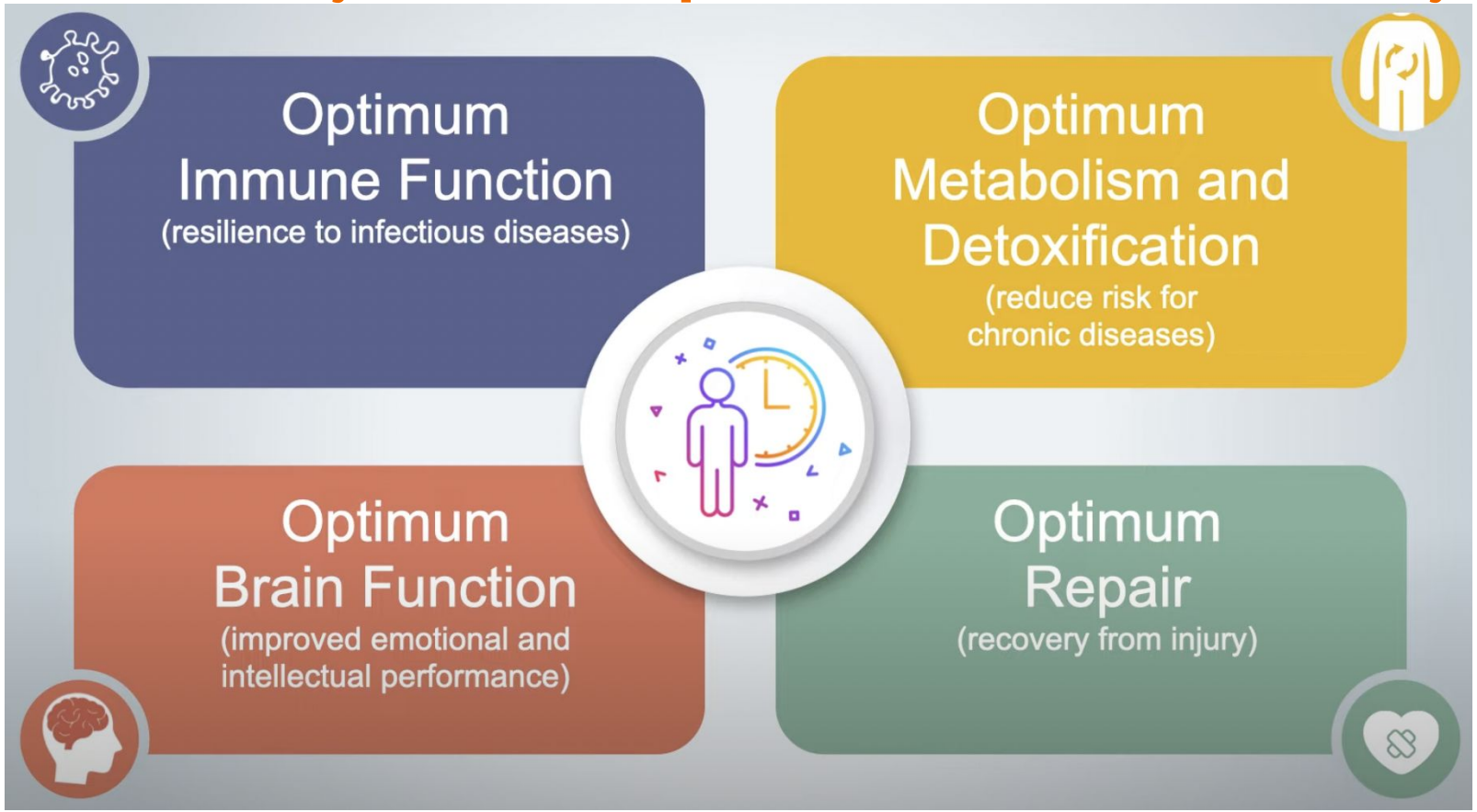
Get to know your class



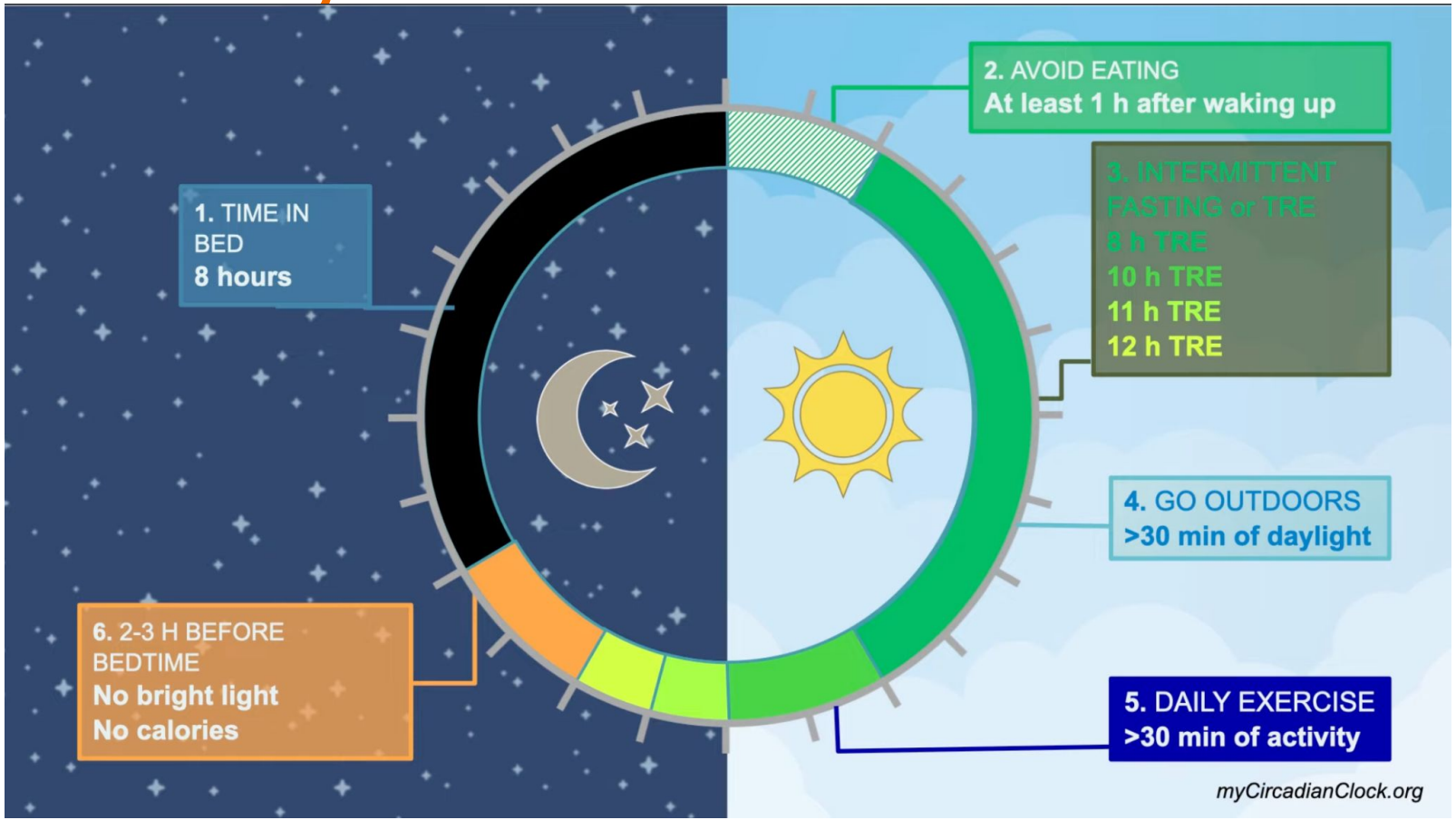
- Are there any bona fide circadian biologists here?
- What model organisms do we all work on?
- What reasons do we have for taking this course?

Day 1: Why do circadian rhythms matter?

Circadian rhythms underpin health in numerous ways



Circadian rhythms can be reinforced or interfered with



Day 1	Day 2	Day 3
Introduction to what circadian rhythms are and how they are maintained	Examination of the effects of circadian rhythm disruptions on health	Exploration of policies related to circadian rhythms

Course Schedule

Day One

- What are circadian rhythms, and why do they matter?
- Autoinhibitory transcriptional networks allow for temporal gene regulation
- How environmental stimuli like light can “entrain” the circadian clock
- How the brain coordinates circadian rhythms in the periphery

Day Two

- How does circadian biology impact shift workers?
- Shift work as a historical phenomenon
- How to leverage circadian biology to improve health outcomes in shift workers
- Exploring the psycho-social ramifications of shift work

Day Three

- How should future policies (DST, school start times) be informed by circadian biology?
- The current status of DST and school start times in the USA
- How to better support health and productivity outcomes using circadian biology

Learning Objectives

At the end of Day 1, students can ...

- ❏ define circadian rhythms and entrainment in layman's terms.
- ❏ outline the steps in the autoinhibitory transcriptional network that creates circadian rhythms.
- ❏ draw out the path through which light, an external cue, entrains the SCN.
- ❏ predict the effect on circadian rhythms if exposed to light during early and late night.
- ❏ explain the role of melatonin as an external cue to entrain the clock.
- ❏ identify peripheral clocks and the bodily functions they regulate.

Think-Pair-Share:

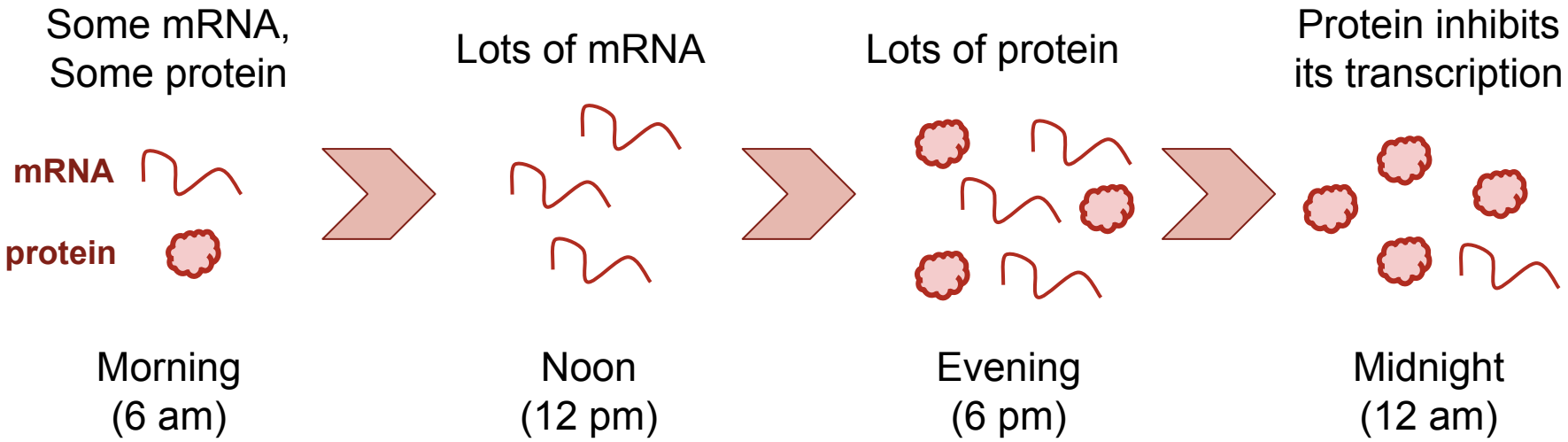
How would you define circadian rhythms for the public?

Take 2 mins to discuss with a partner then I'll ask for volunteers.

How would you define circadian rhythms for the public?

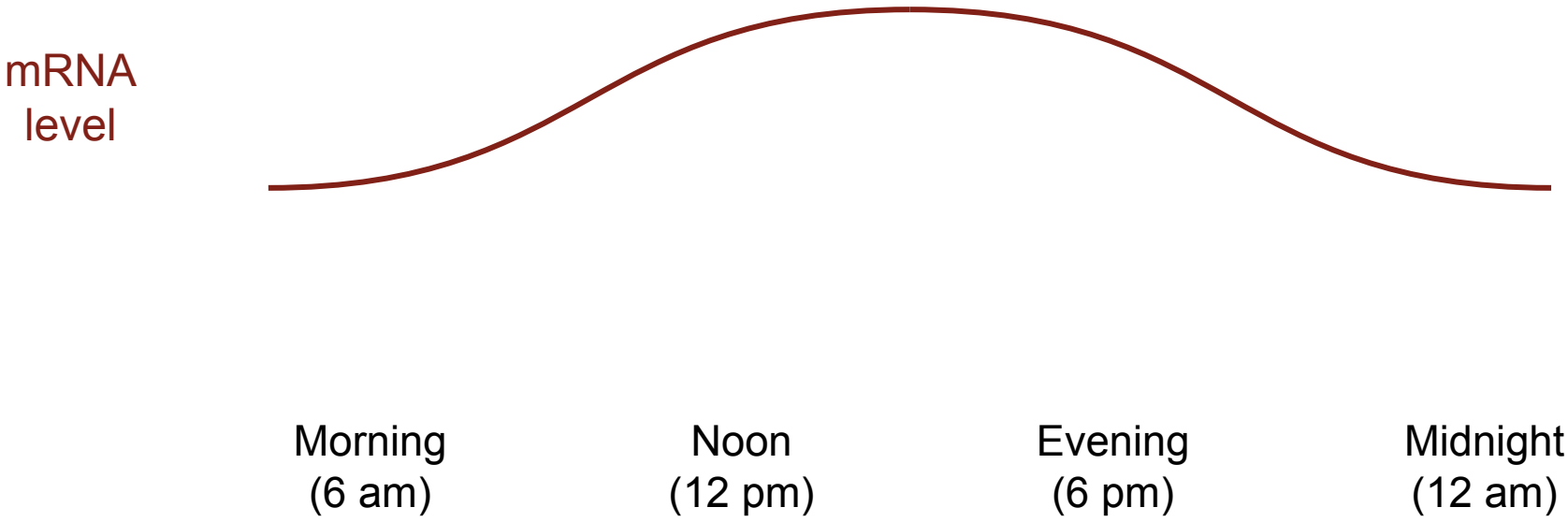
How does a cell keep track of time?

Big idea: cells use an auto-inhibitory transcriptional feedback loop, in which proteins are transcribed, feedback to inhibit their transcription, and then degrade over a ~24 hr period to regulate circadian rhythms.



How does a cell keep track of time?

Levels of mRNA or protein correspond with time of day.



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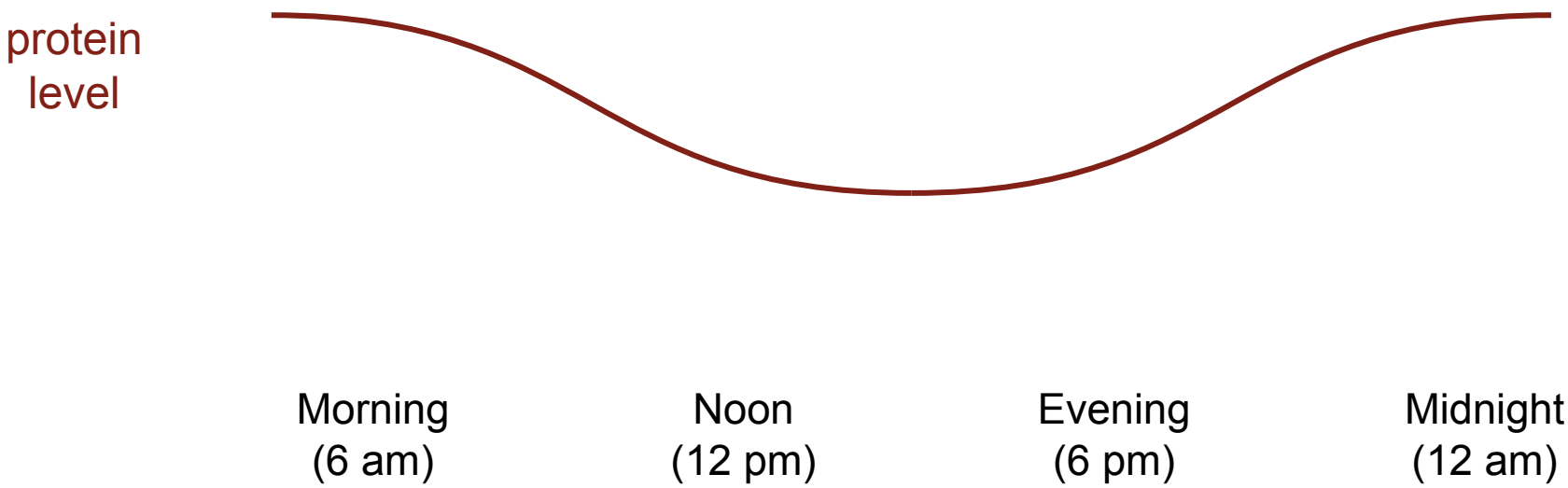


Pairs of genes and proteins regulate circadian rhythms

PROTEIN / *gene*

PER / *per*

CRY / *cry*

BMAL1

CLOCK

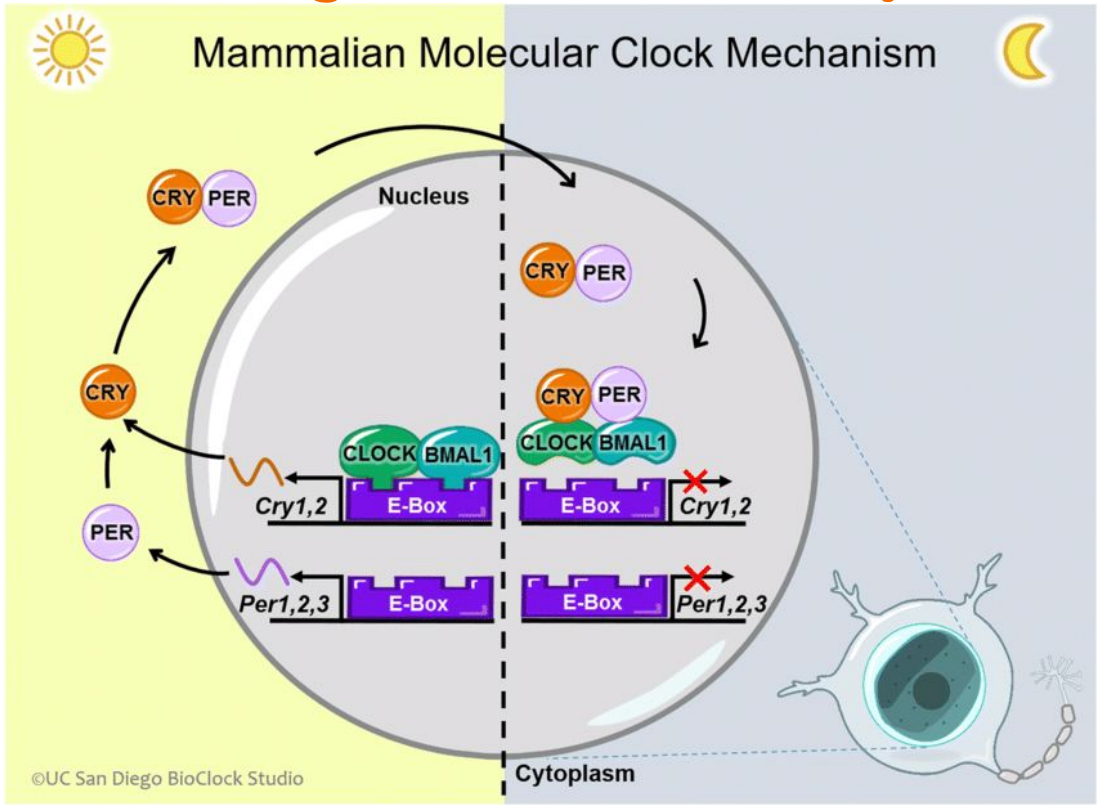
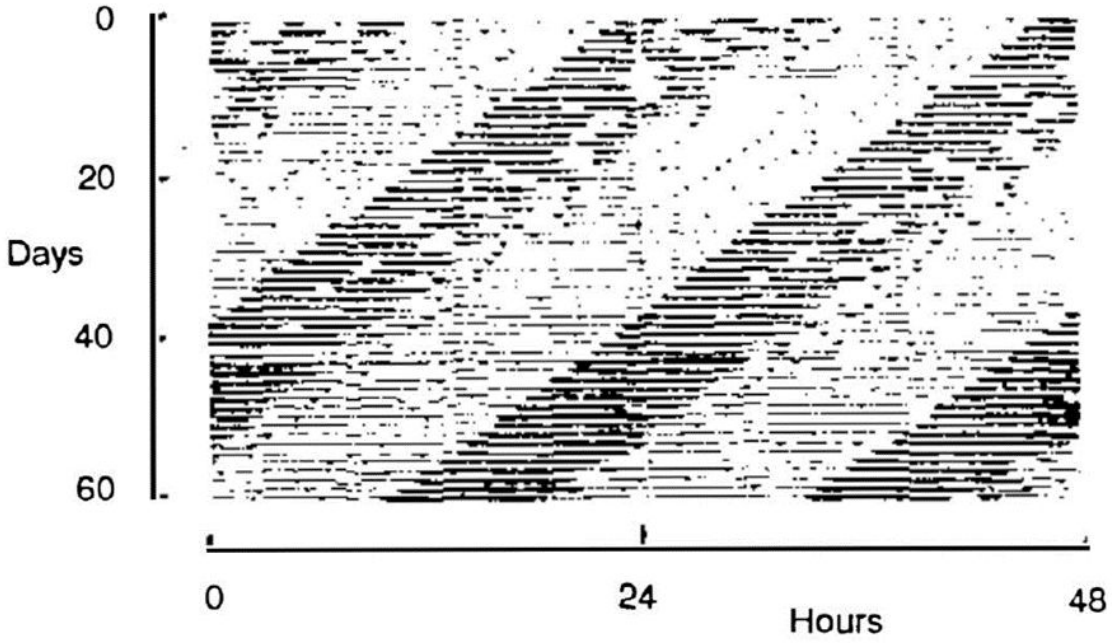


Image source: Rhoads et al. 2020

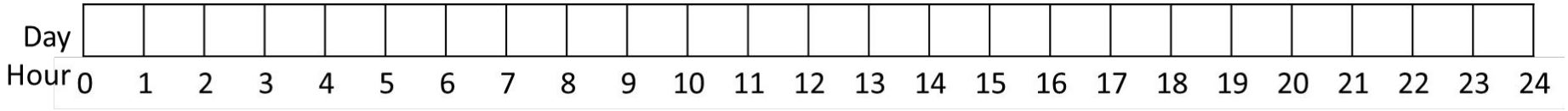
Worksheet:

Work in pairs or small groups to outline the steps of the auto-inhibitory transcriptional network.

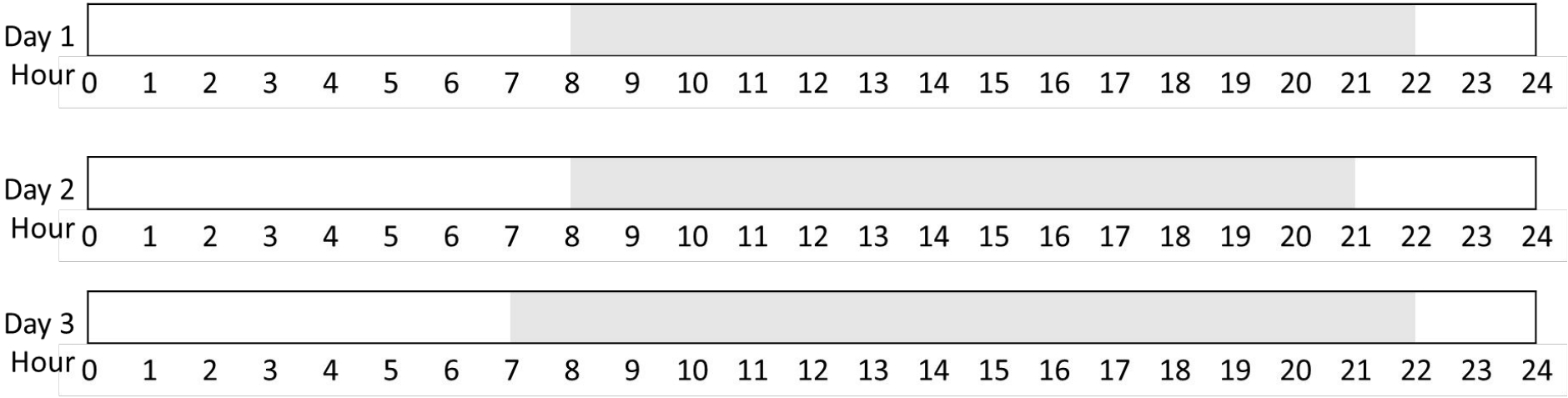
Circadian rhythms can be represented as actograms



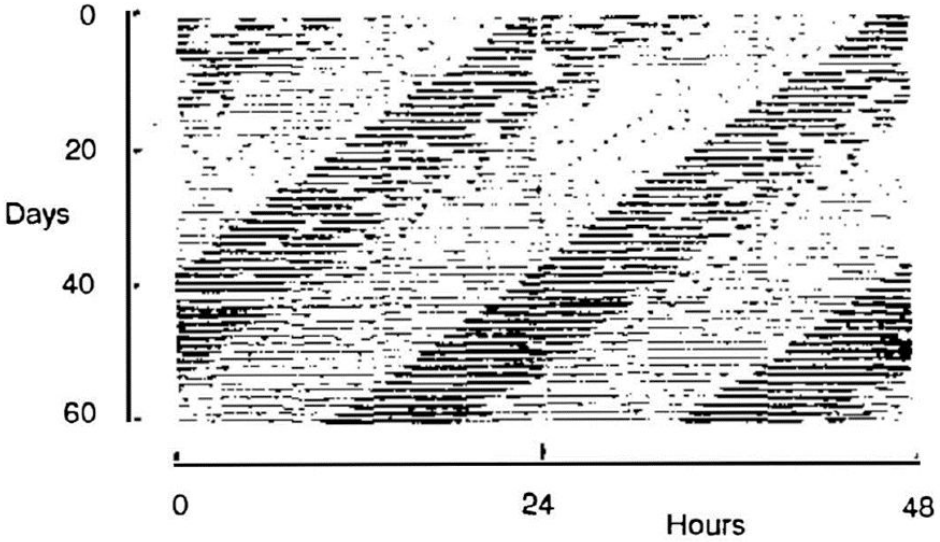
Circadian rhythms can be represented as actograms



Shaded bars are periods of activity and white bars are period of rest

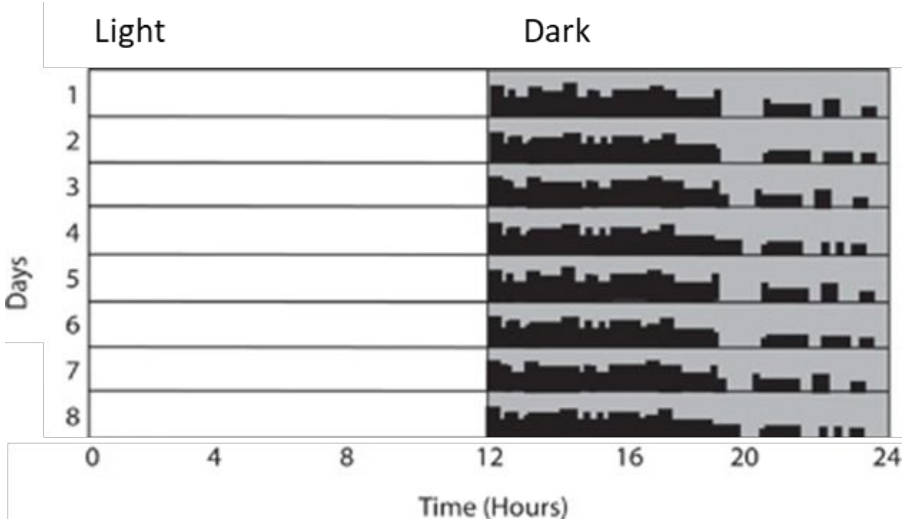


Circadian rhythm is < 24h in constant darkness



Actogram of mouse in constant darkness

Circadian clocks can be entrained by external cues

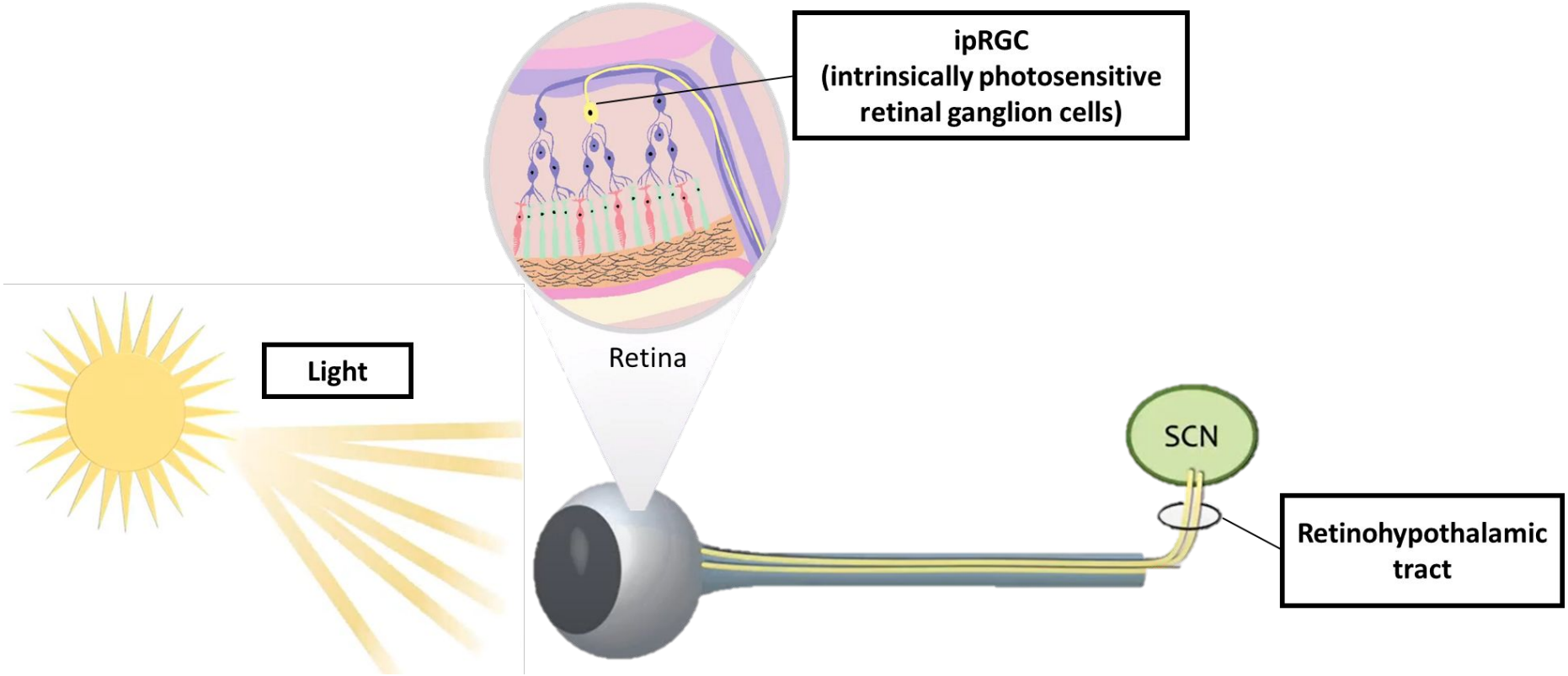


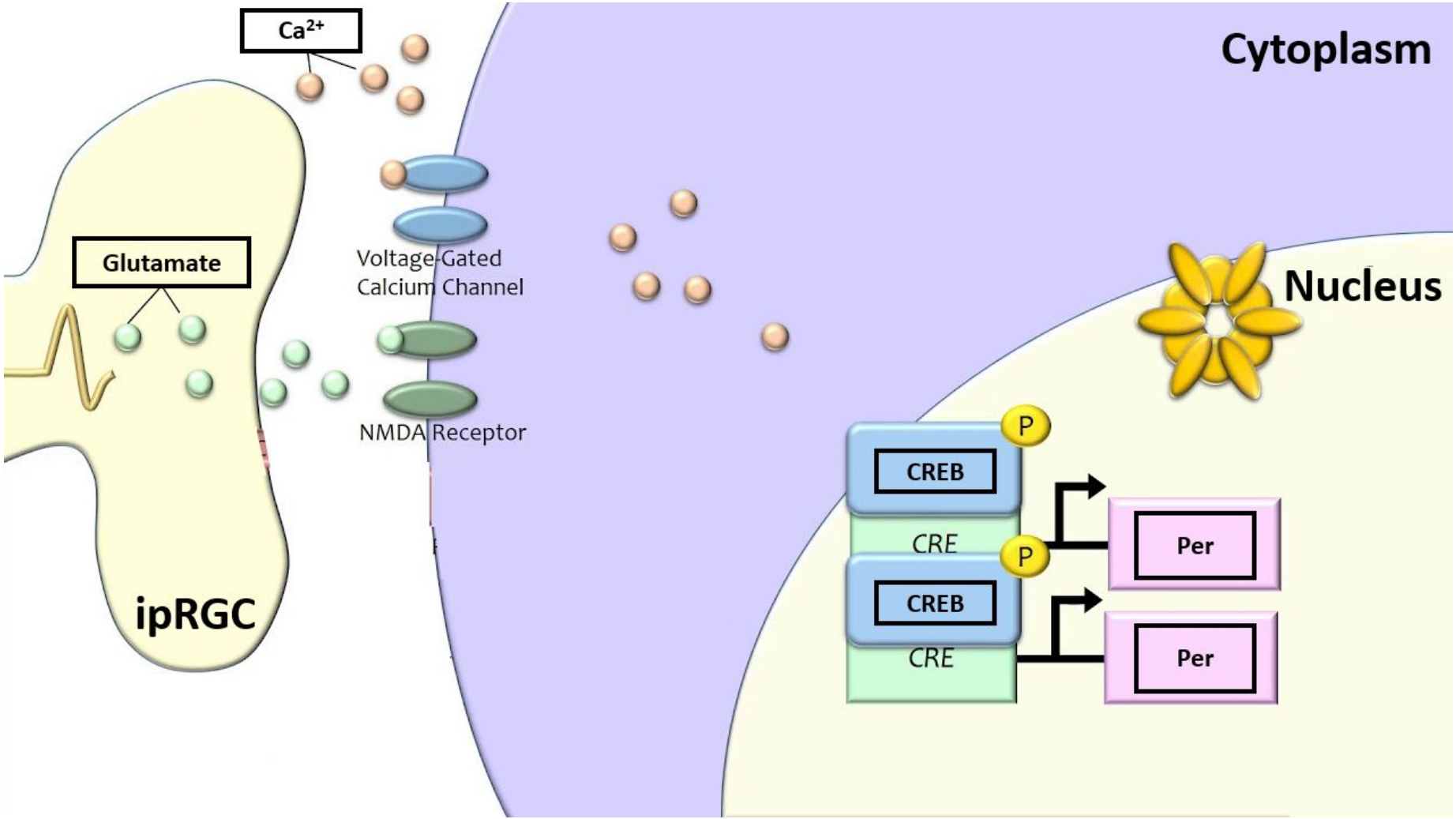
Actogram of mouse in 12:12 Light:Dark

Poll Everywhere:

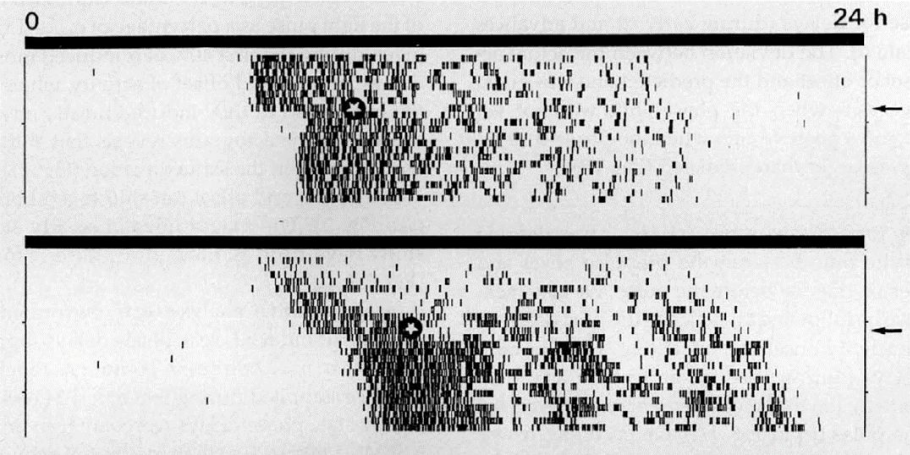
How would you define entrainment of the circadian rhythm for the public?

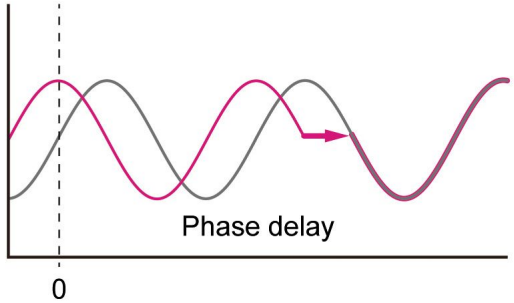
How would you define entrainment of circadian rhythms for the public?


ipRGC
(intrinsically photosensitive
retinal ganglion cells)
Light
Retina
SCN
Retinohypothalamic
tract


Ca2+
Cytoplasm
Glutamate
Voltage-Gated
Calcium Channel
Nucleus
NMDA Receptor
P
CREB
CRE
P
Per
CREB
CRE
Per
ipRGC

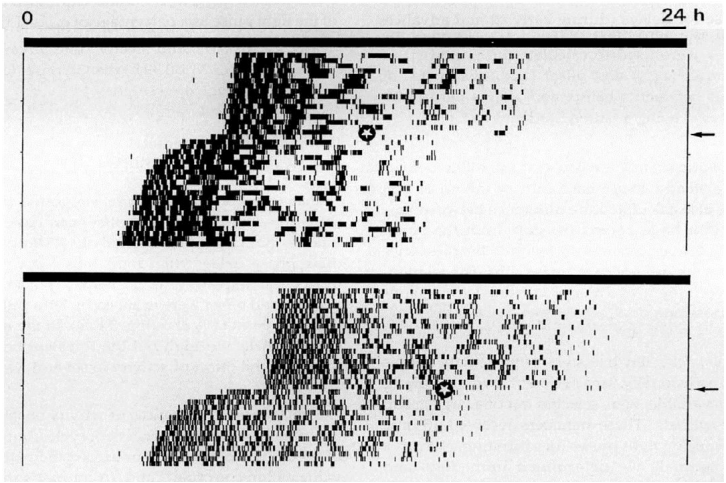
Effects of light on circadian rhythms: Phase Delay

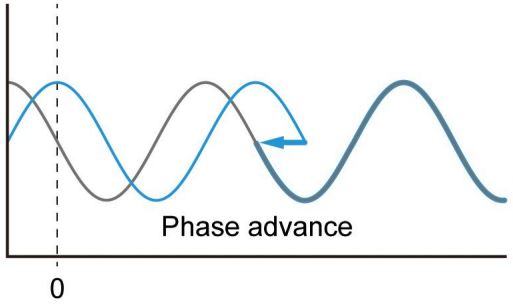




- Occurs when exposed to light during first half of the night
- Activity starts **later** in the day

Effects of light on circadian rhythms: Phase Advance

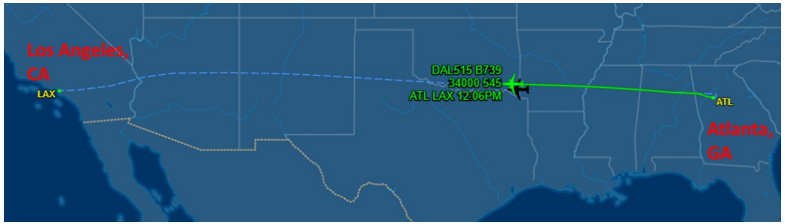




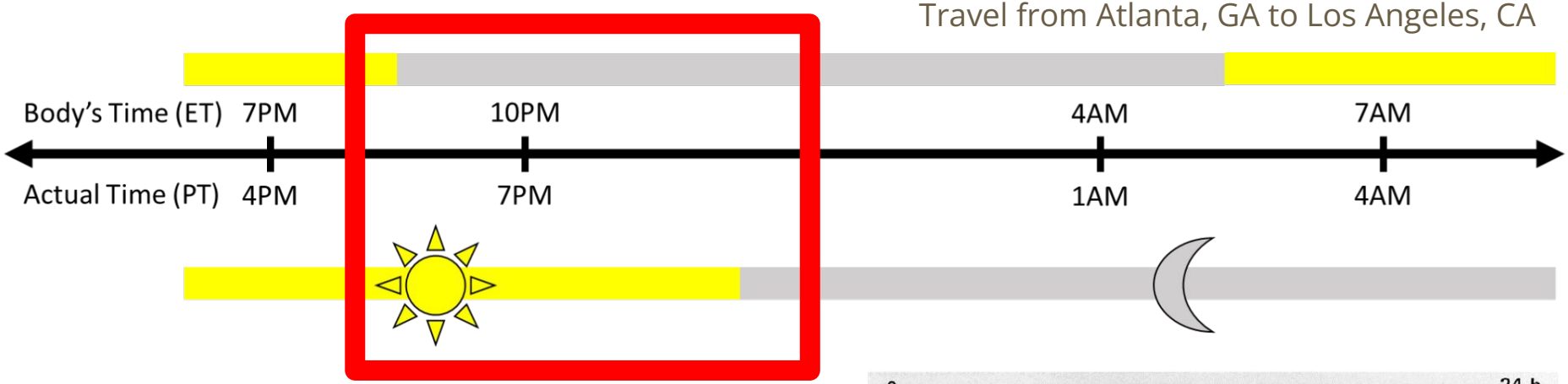
- Occurs when exposed to light during second half of the night
- Activity starts **earlier** in the day

Example of Phase Shift: Jet Lag

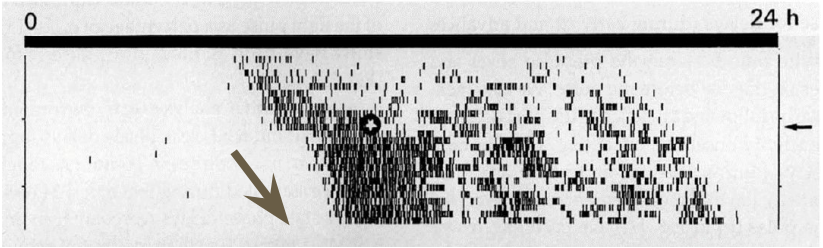
Phase Delay- Travel Westward



Travel from Atlanta, GA to Los Angeles, CA

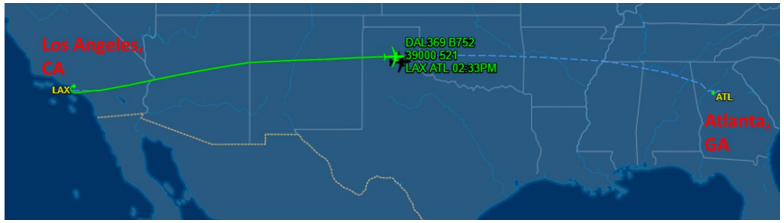


Light exposure in the **first half** of the night.



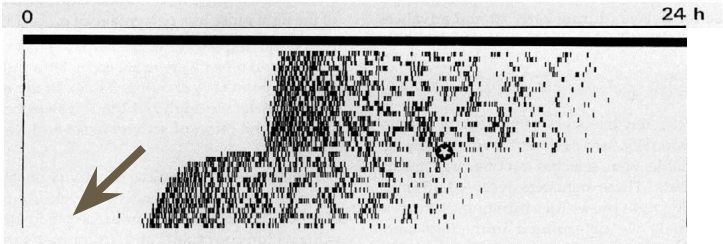
Example of Phase Shift: Jet Lag

Phase Advance- Travel Eastward



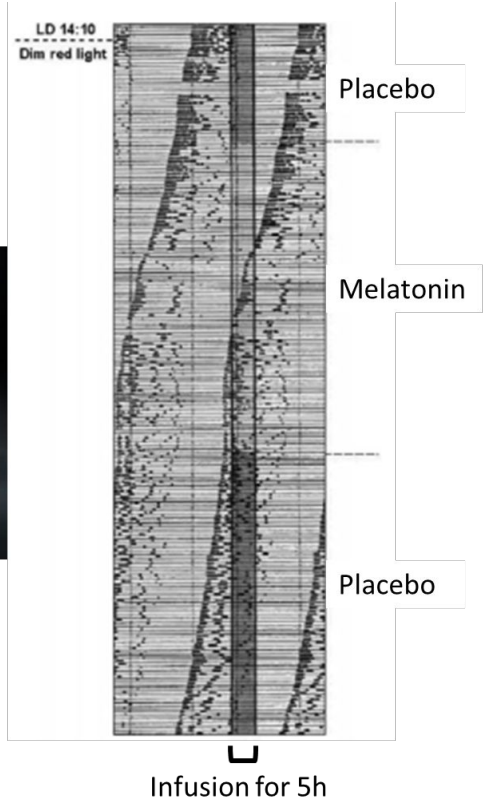
Travel from Los Angeles, CA to Atlanta, GA

Light exposure in the **second half** of the night.



Exogenous melatonin can be an external cue for entrainment…

In constant darkness

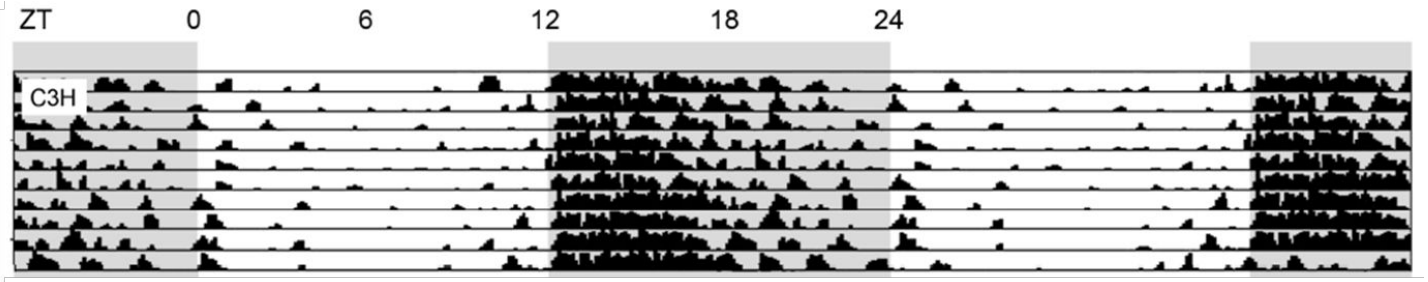


Infusion for 5h

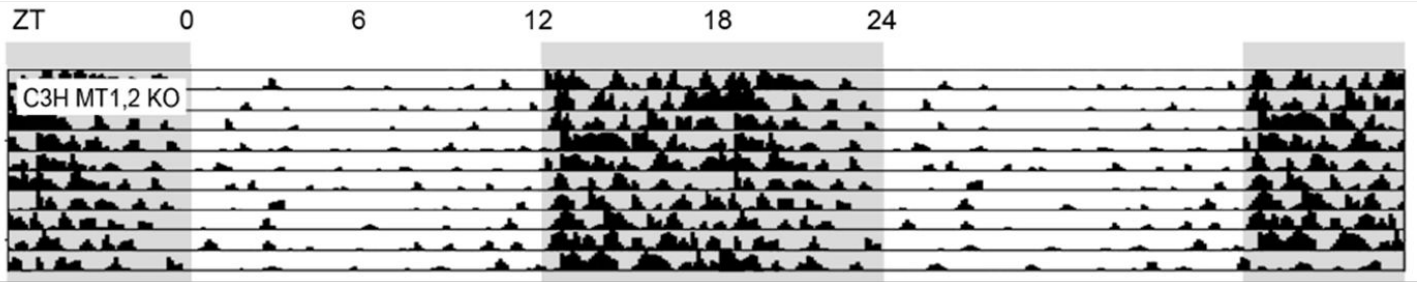
- When placebo was administered, circadian rhythm was < 24h
- When melatonin was administered, circadian rhythm was ~24h
- Once melatonin administration was stopped, circadian rhythm went back to < 24h

… but it is not essential for entrainment

✓ melatonin



✗ melatonin

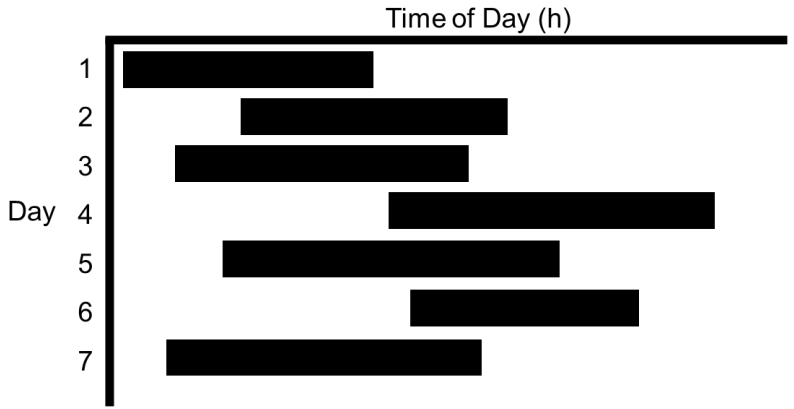


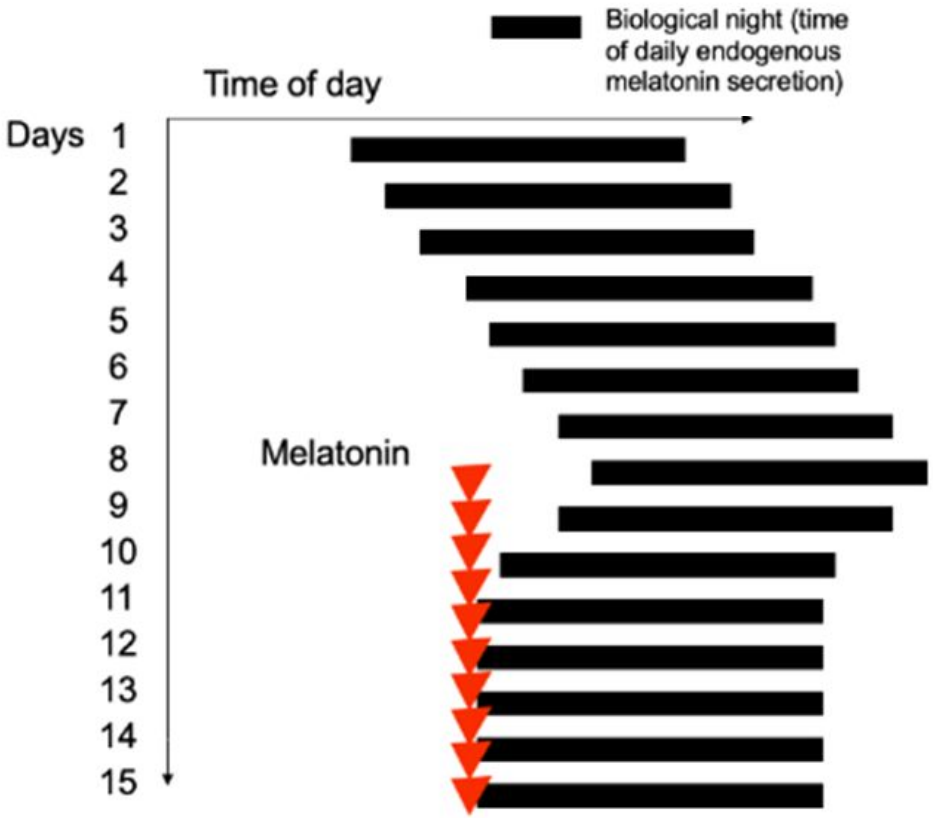
Group Activity:

Sketch a 7-day actogram of a …

- **Scenario 1: completely blind person's circadian rhythm**
- **Scenario 2: completely blind person's circadian rhythm who is taking melatonin**

Example:





Circadian rhythm of a completely blind person

- SCN is not entrained by light
- Circadian rhythm is not 24h

Circadian rhythm of a completely blind person taking melatonin before bed

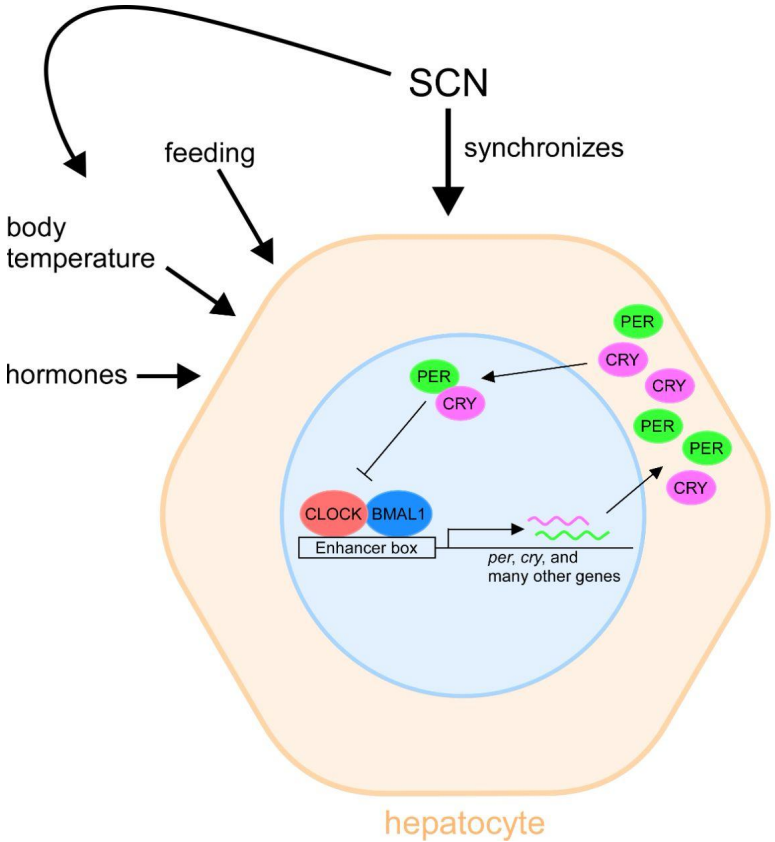
- SCN is entrained by melatonin
- Circadian rhythm is 24h

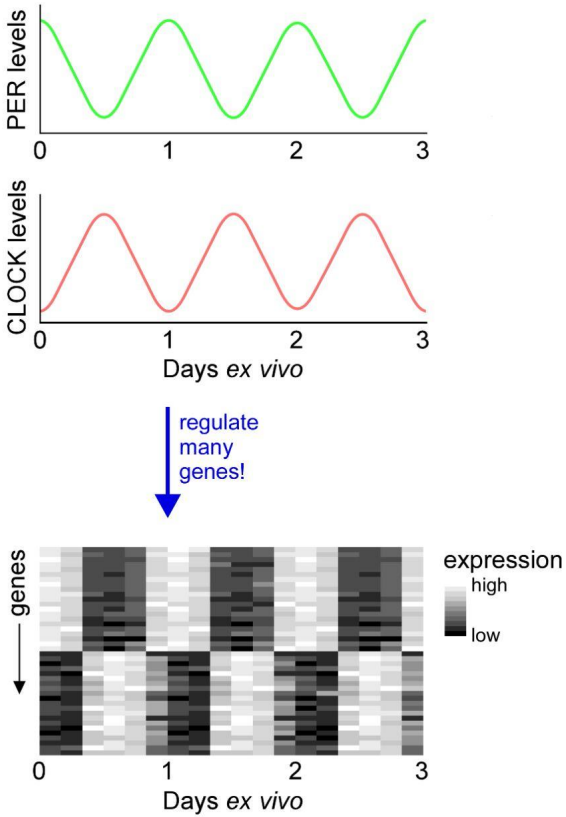
Clocks are everywhere!

- While the master timekeeper is in the brain, many cells in your body change their activity according to the time of day.
- While the brain contains the master timekeeper that can inform processes in the periphery, almost every cell in the body has its own clock!

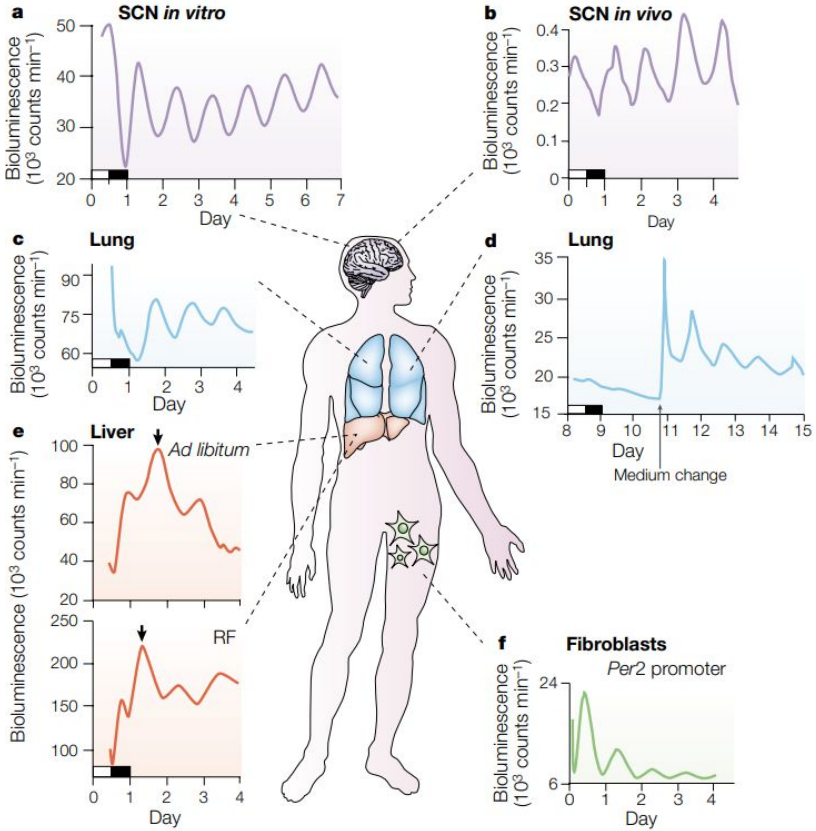
Where in the body would you expect to find circadian rhythms?

What is a peripheral clock?





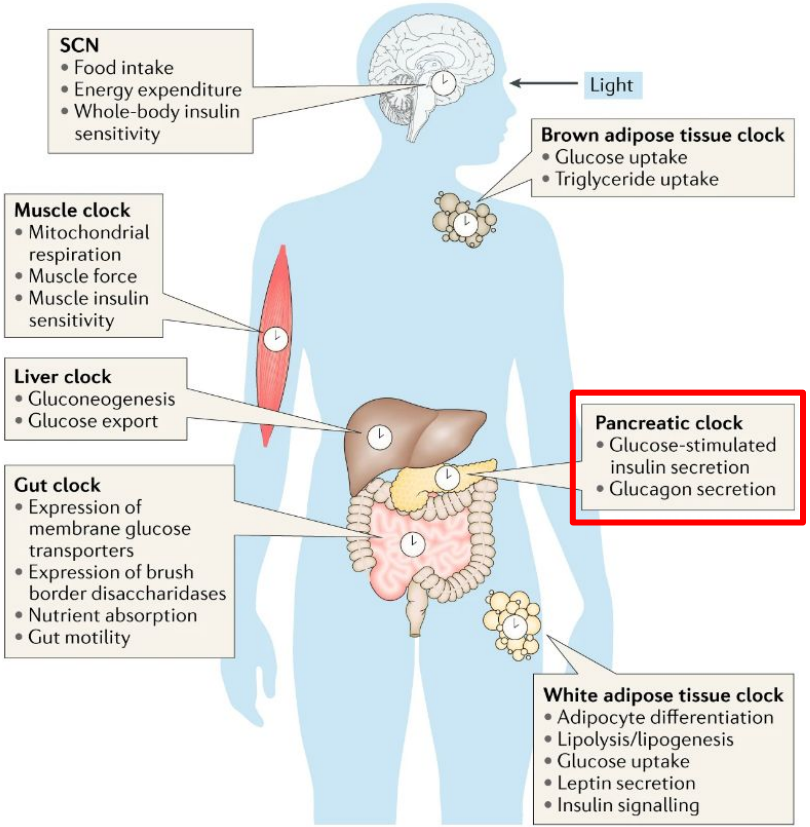
Nearly all tissues in the body have peripheral clocks.

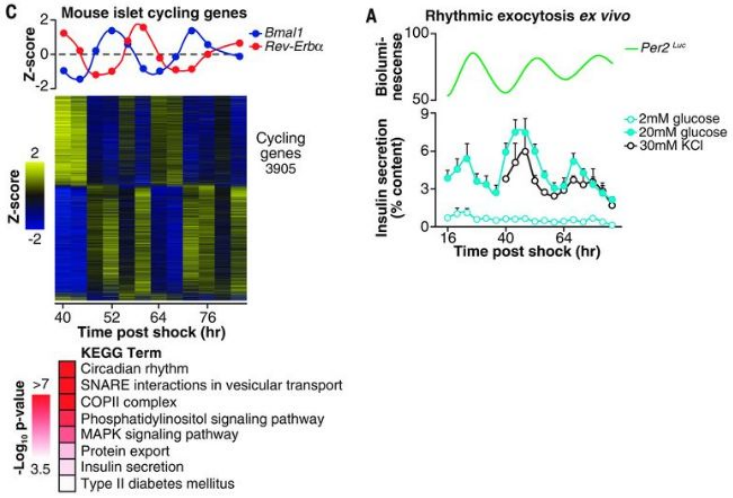


Hastings, M. H., et. al. (2003) *Nat. Rev. Neurosci.*

Other examples: immune system, heart, vasculature, bone, gut, pancreas, muscle, other brain regions, etc.

Peripheral clocks regulate metabolism.

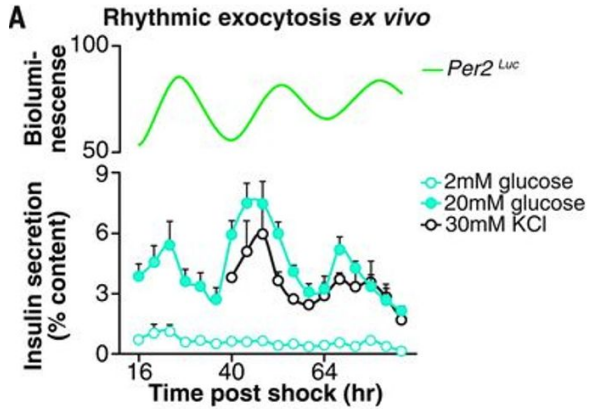




Stenvers, D. J., et. al. (2019) *Nat. Rev. Endocrinol.*

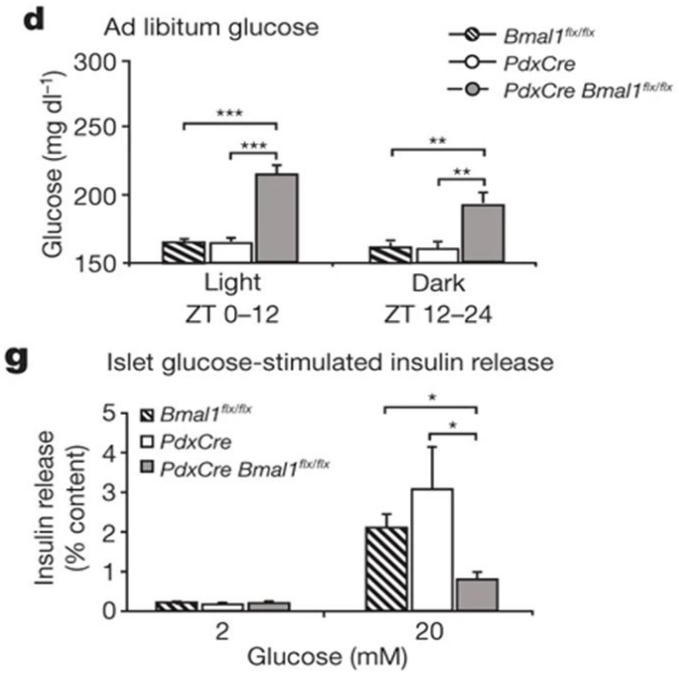
Perelis, M., et. al. (2015) *Science*.

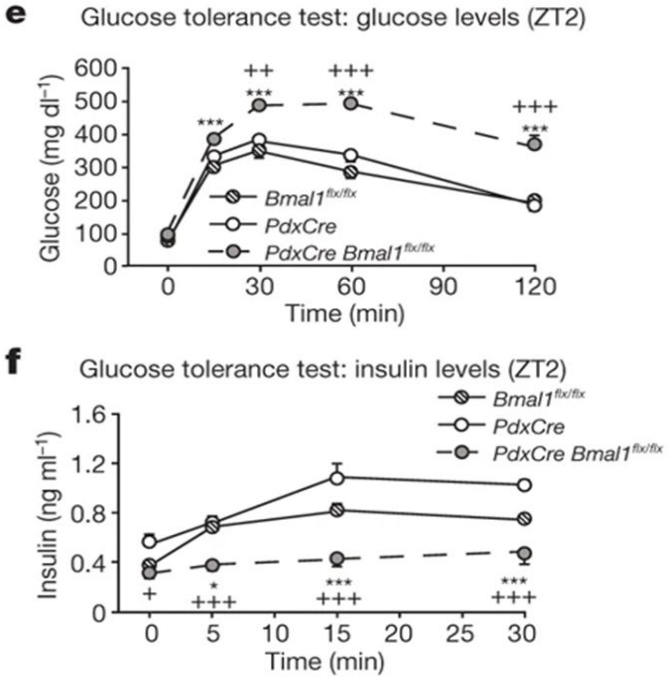
Predict how deleting the peripheral clock **from only the pancreas** will change insulin secretion and blood glucose levels in mice. Discuss with a partner for 2 min before we discuss as a group!



Perelis, M., et. al. (2015) *Science*.

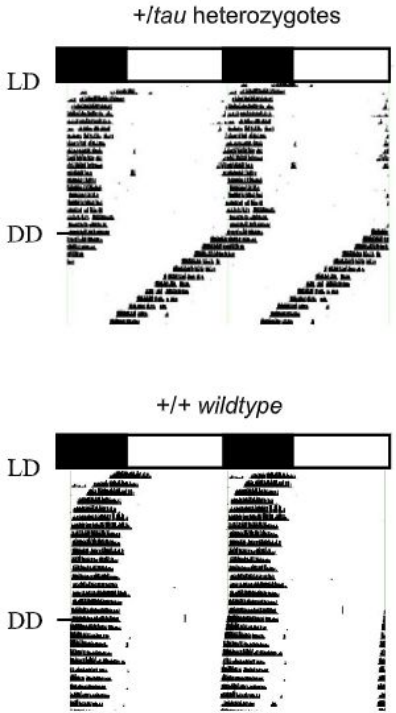
the result is diabetes!

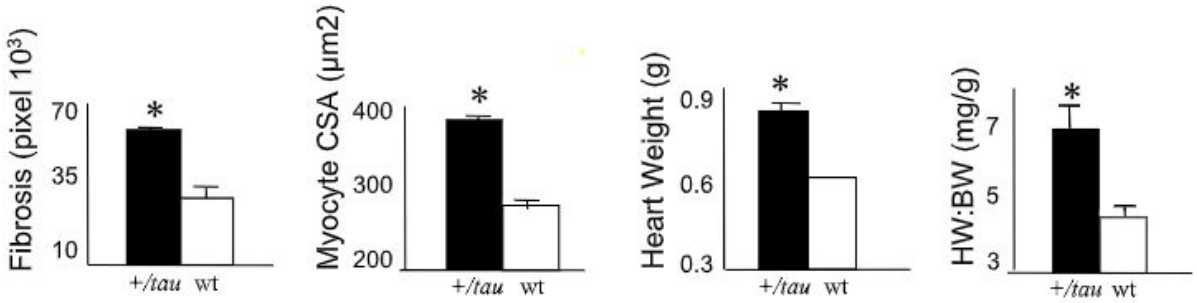




Marcheva, B., et. al. (2011) *Nature.*

Chronic mismatch between genotype and LD cycles causes scarring and enlargement of the heart in hamsters.

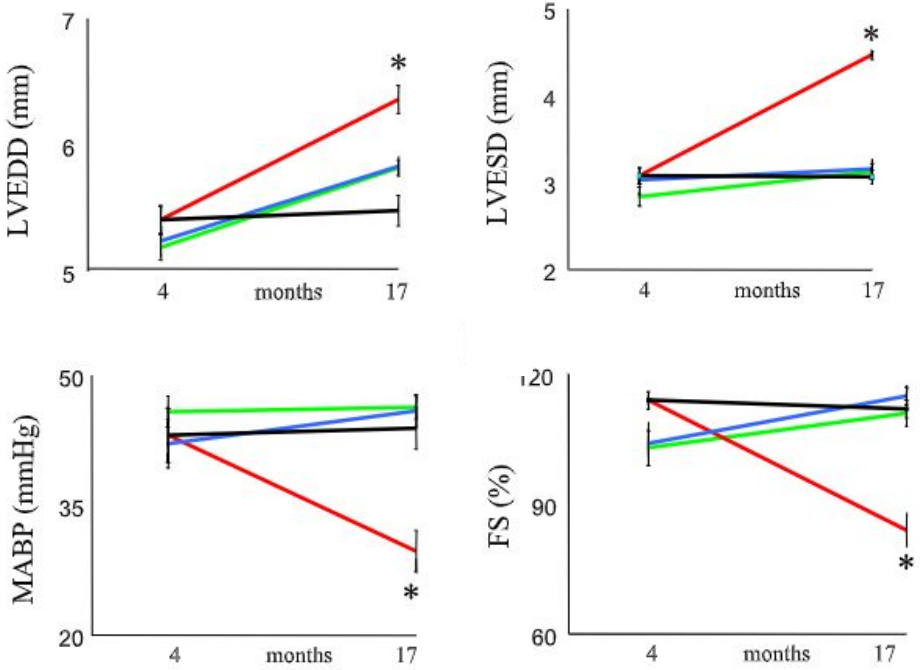




+/tau hamsters have a **shorter circadian rhythm (22h LD cycle)** than WT animals (24h)

Martino, T. A., et. al. (2008) *Am. J. Physiol. Regul. Integr. Comp. Physiol.*

Cardiovascular defects can be rescued by switching +/tau hamsters to a 22h LD cycle!



Black: WT
Blue: tau/tau
Red: +/tau, 24h LD
Green: +/tau, 22h LD (rescue)

Martino, T. A., et. al. (2008) *Am. J. Physiol. Regul. Integr. Comp. Physiol.*

What is one new thing you learned today?