What is interesting about circadian rhythms: background, human biology biochemistry and then a couple of tangential thoughts

We Will Dream With Our Eyes Open

17th Annual GoldLab Symposium

May 14-15, 2026

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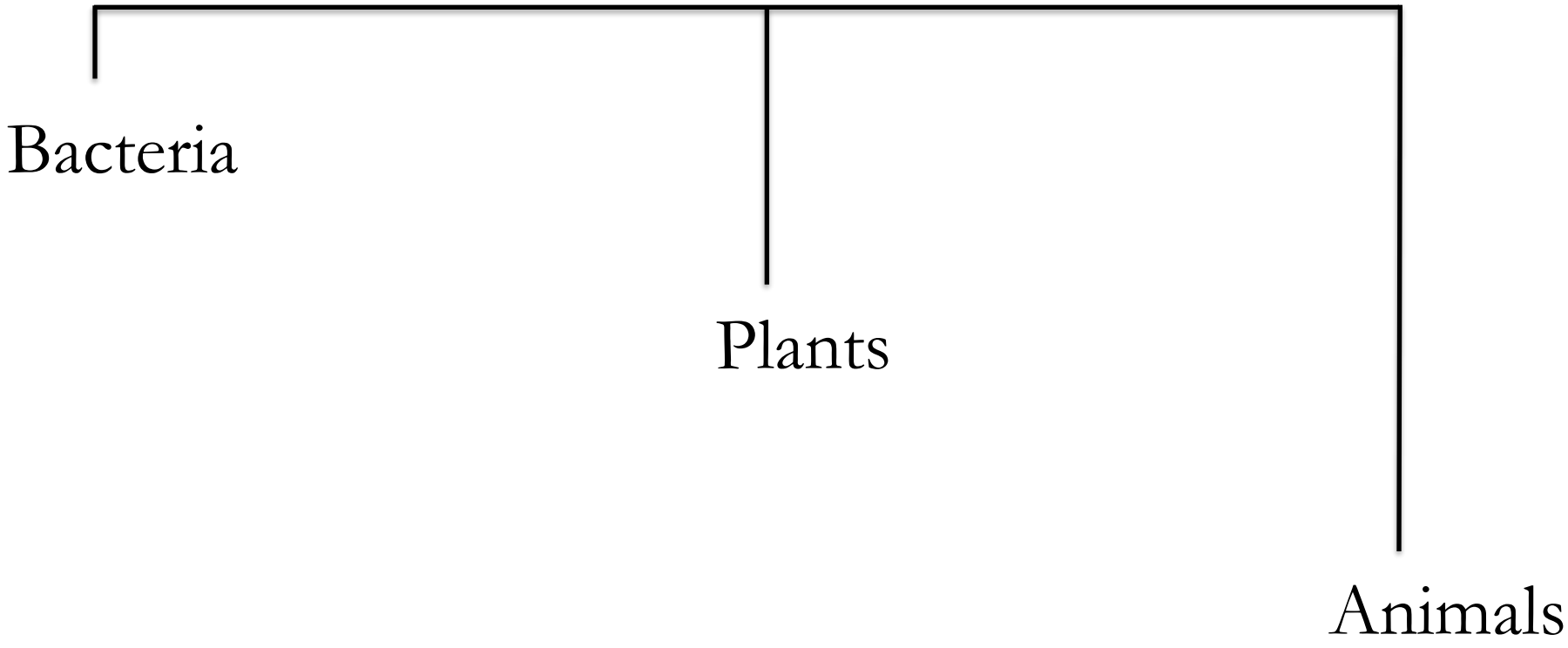
- **Nick Petersen**
- Shlesha Richhariya
- Muskan Shah
- Camille Sullivan

Undergrads

Alisha Anderson
Georgie Balogun
Emma Liu
Max Tsai
Zimo Zhang

Circadian rhythms arose long ago as adaptations to the rotation of the earth

Circadian clocks are very different in different kingdoms, suggesting multiple origins during this more than 1.5 billion years of evolution



Circadian Rhythm Properties

- Self-sustained: Keeps ticking in darkness with a species-specific non-24.0 period.

  (circa dia)

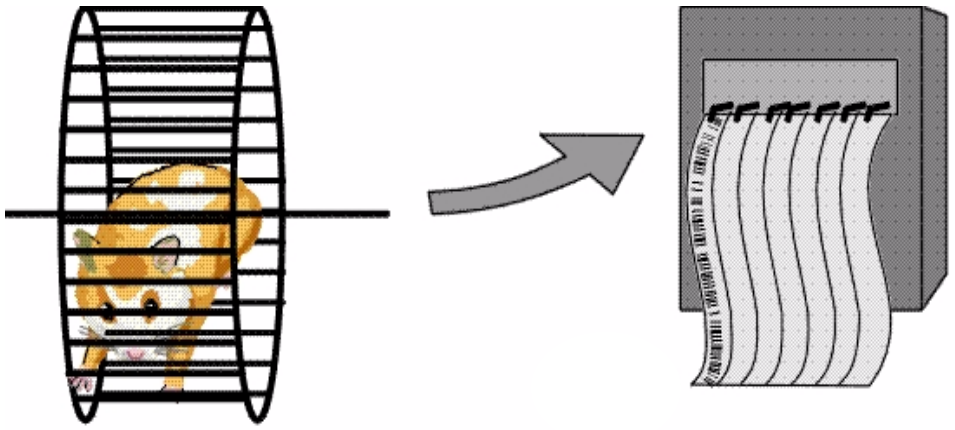
- Entrains to the light cycle. Now exactly 24hrs.

- Purpose: Anticipation

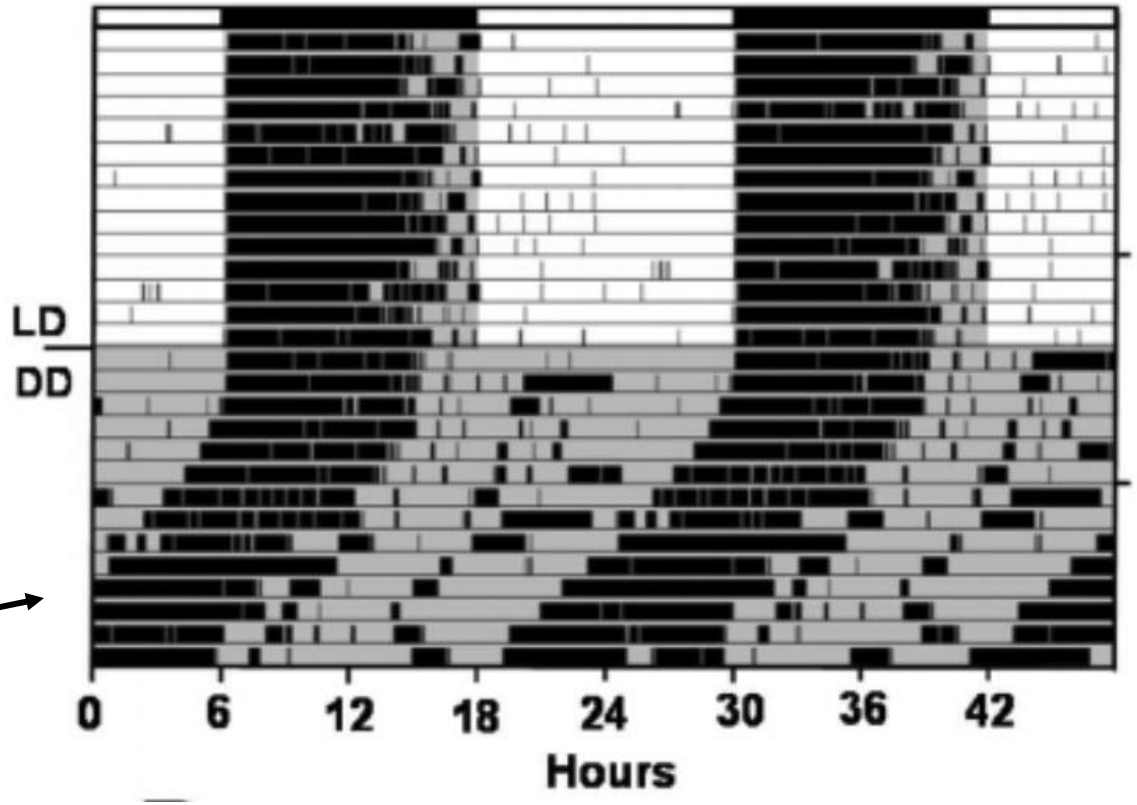
- Internal purposes also

Sidney Brenner: “Progress in science depends on new **techniques**, new **discoveries** and new ideas, probably in that order.”

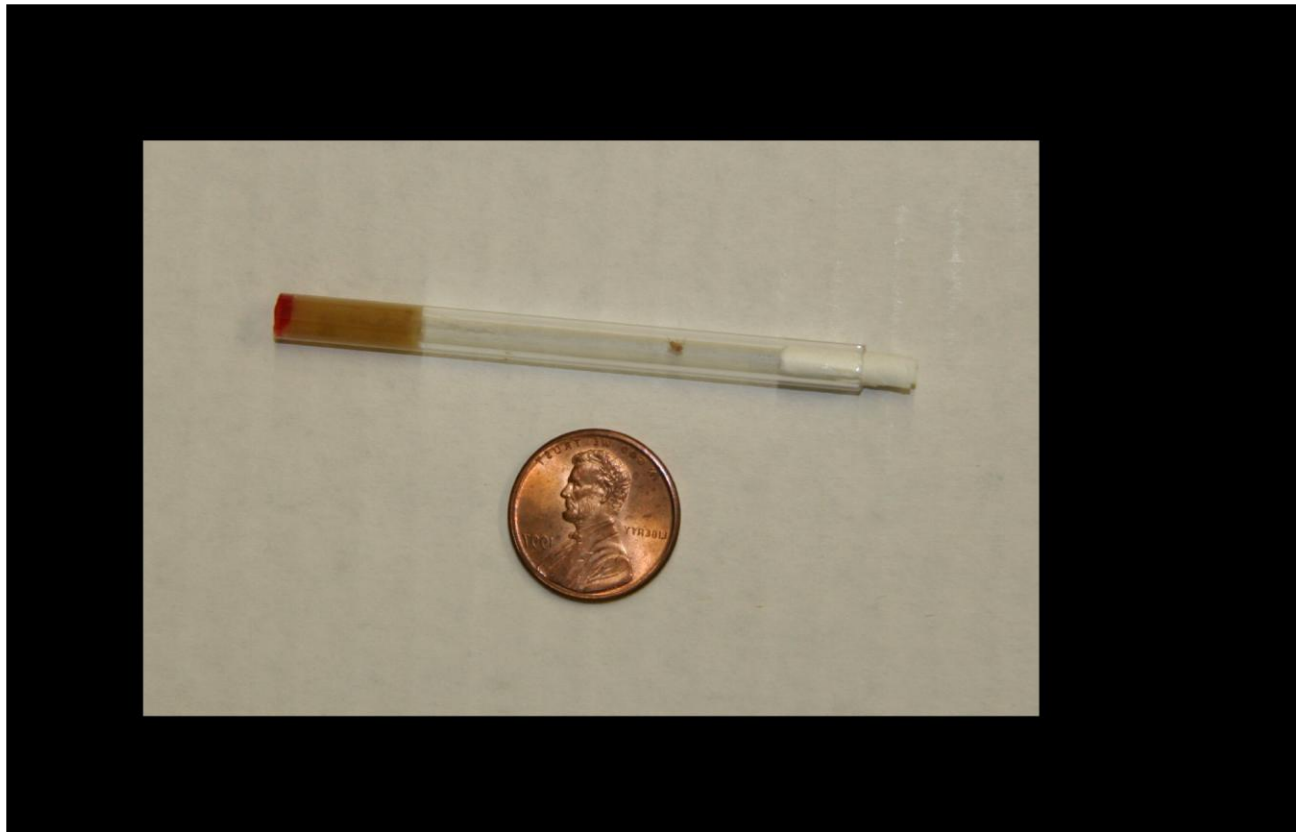
The assay, precision and reproducibility of animal locomotor activity is a remarkable circadian/behavioral **technique** as well as a **discovery**

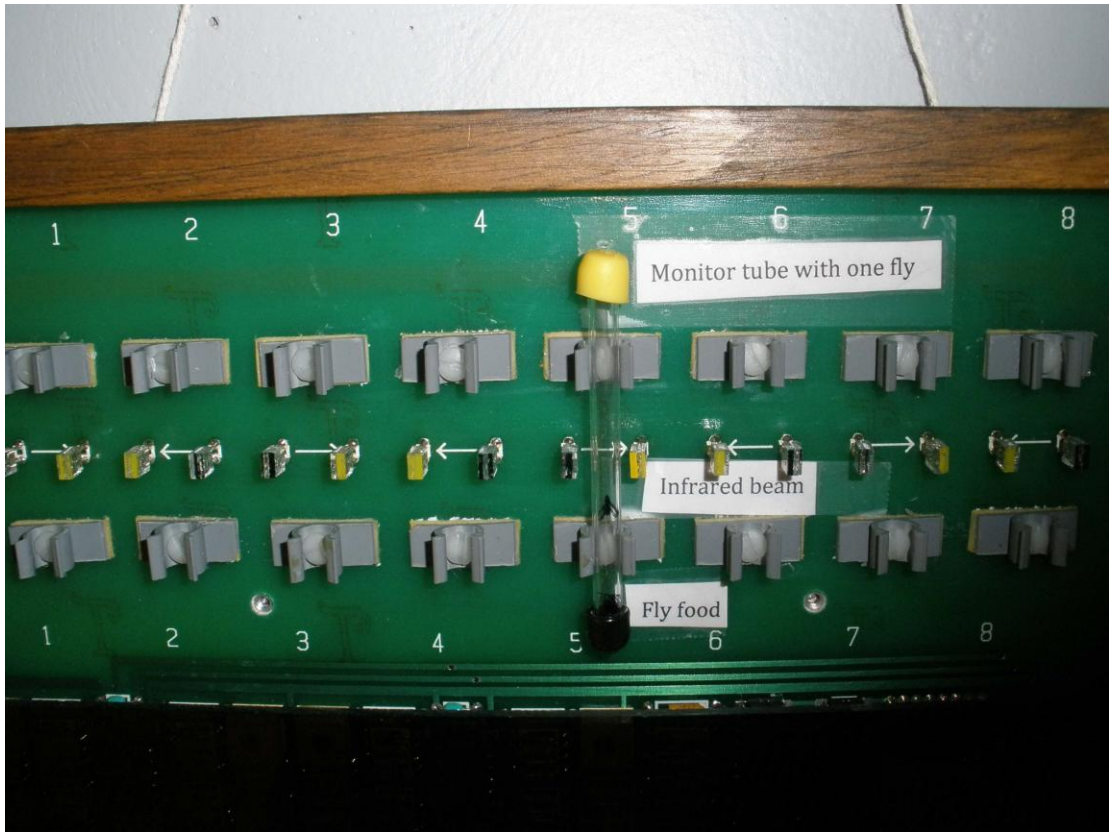


species-specific free running period
every animal is essentially identical



Locomotor activity assay of flies and our original monitoring device

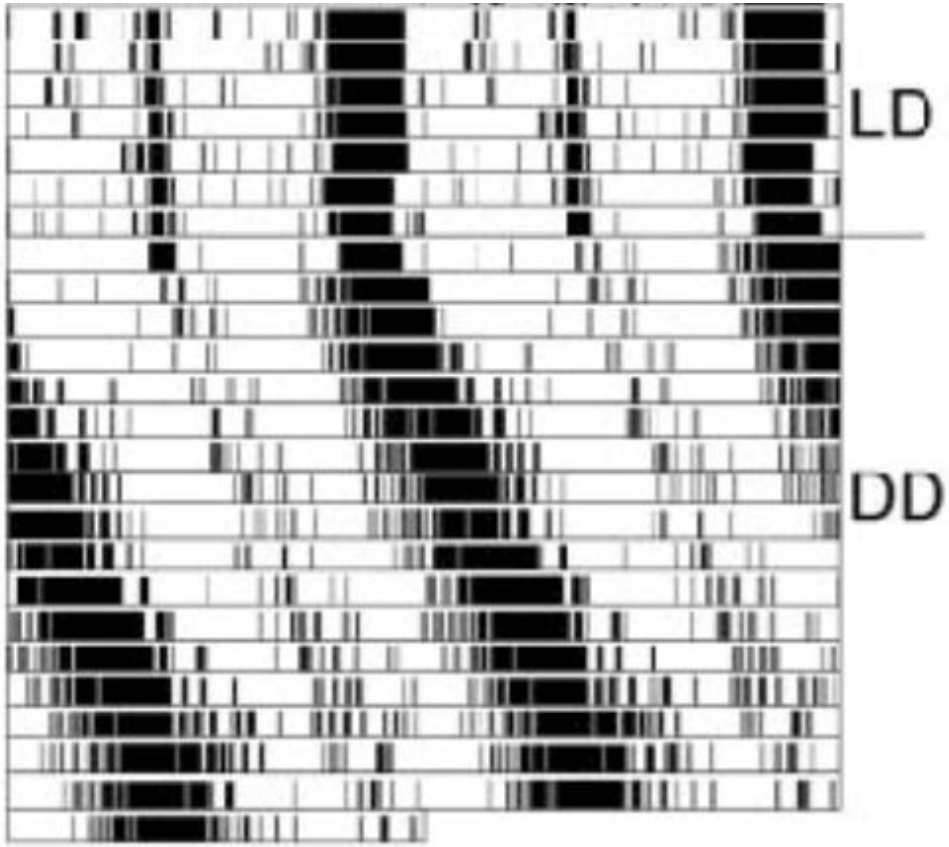




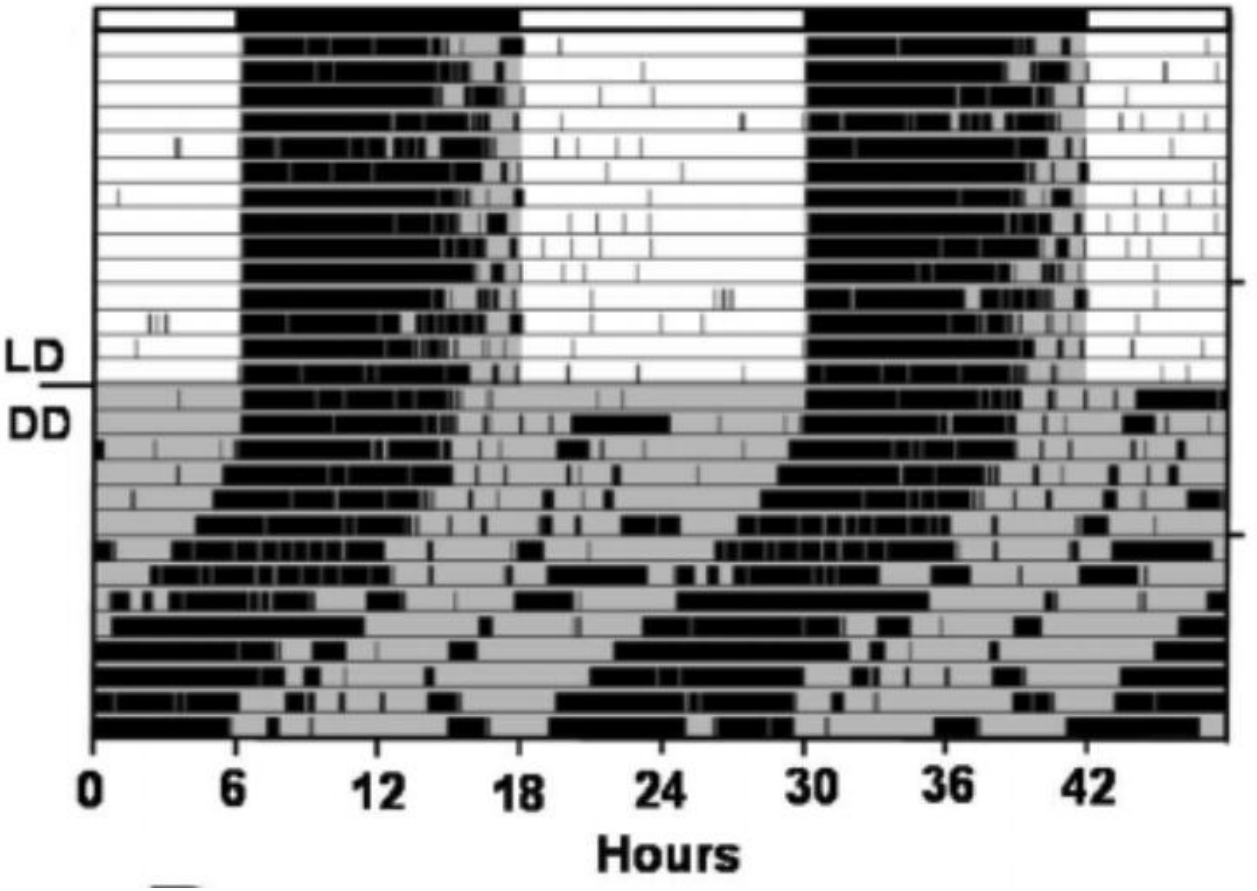
Fly and mouse activity records have similar features

“phenotype, phenotype, phenotype”

Flies

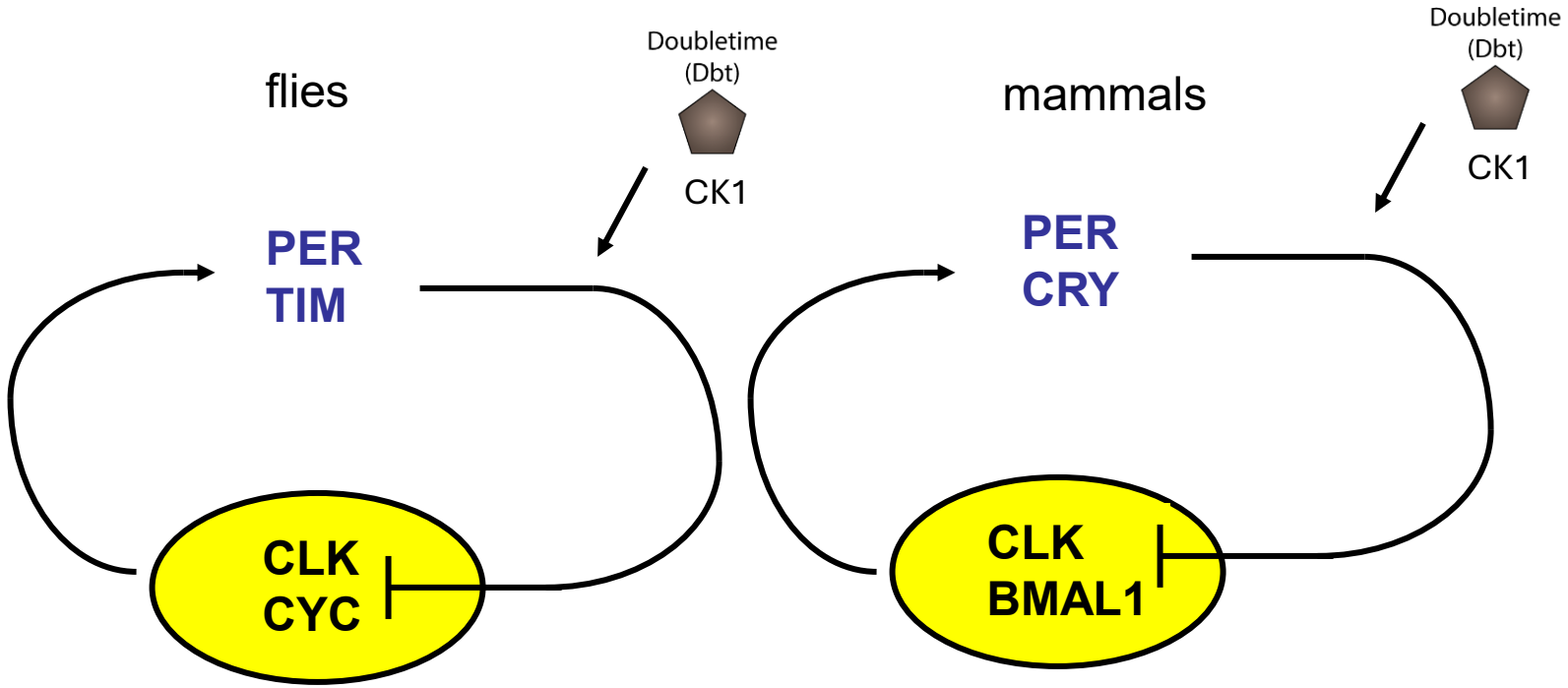


Mice



Fly genetics, cloning, molecular biology and mouse genetics revealed this conserved circadian negative feedback loop

(1998-2026)



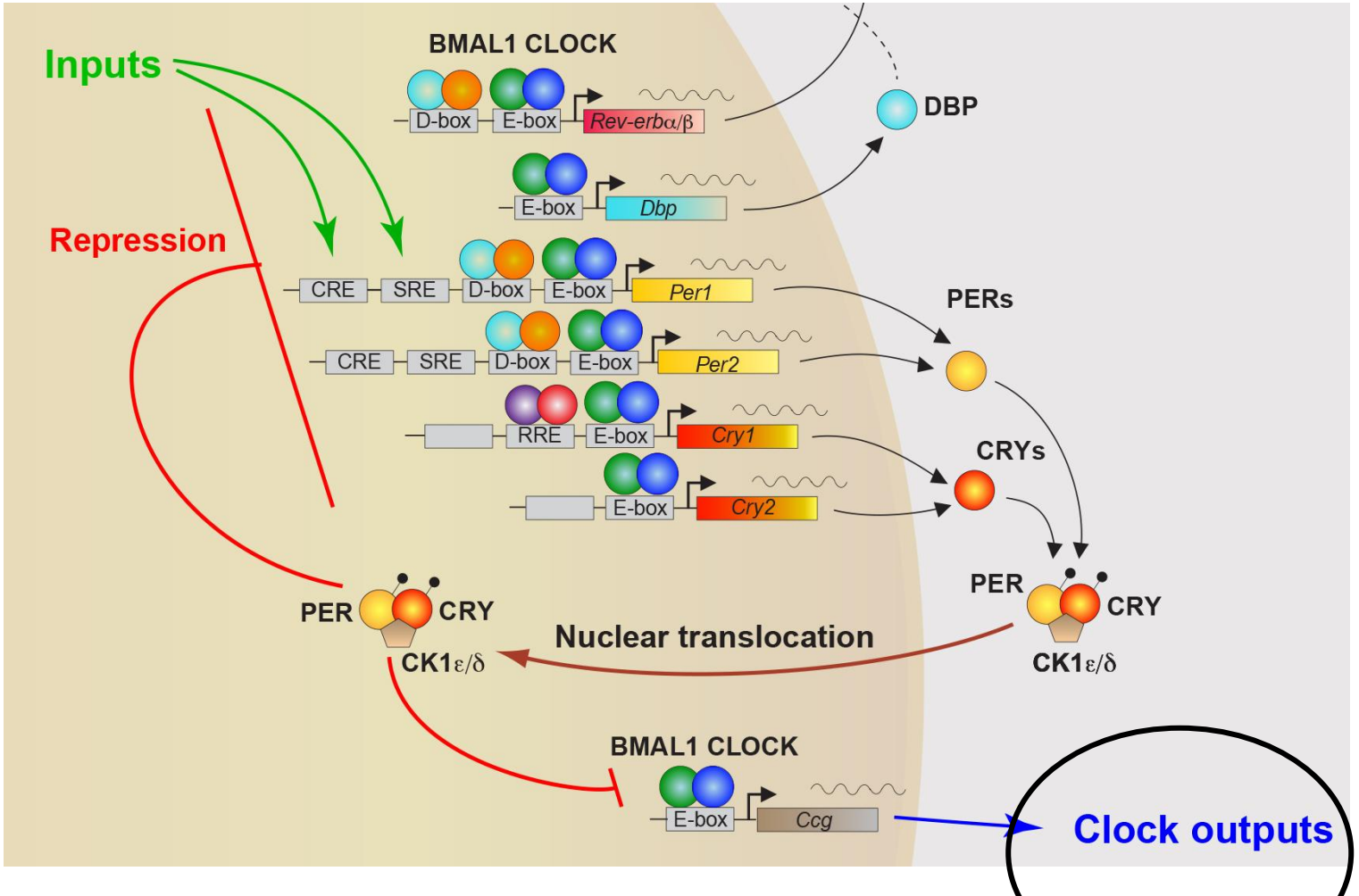
A challenge: leveraging the impact of circadian rhythms on physiology and metabolism to improve human health

- Metabolic Diseases, e.g., metabolic syndrome and diabetes.
- Cancer
- Sleep.
- Drug or Treatment Efficacy. Pharmacokinetics. Medicine…
- Seasonal Affective Disorders (Depression?)
- Shiftwork.
- Jet Lag.

Why does the circadian clock have such a profound influence on physiology and metabolism?

The core clock mechanism ticks away in most if not all tissues

Moreover, the core clock mechanism orchestrates the circadian cycling of hundreds to thousands of different mRNAs in almost every tissue



As a consequence, a large fraction (>70%) of mammalian genes are expressed rhythmically in at least one tissue/cell type

Hence the broad reach of the circadian clock over almost all aspects of physiology and metabolism

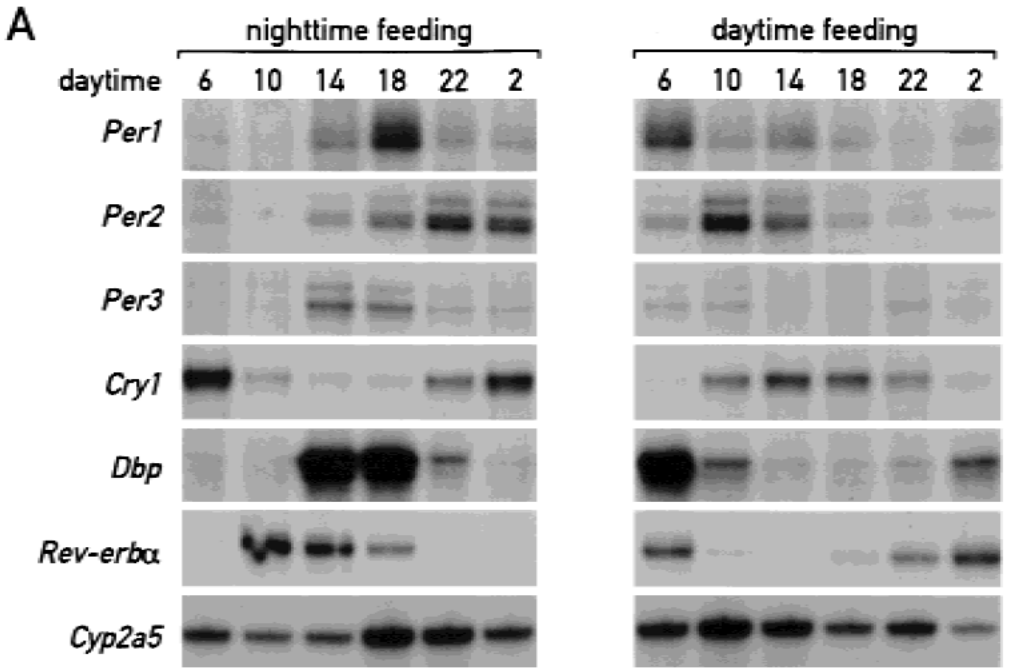
Chronopharmacology
or
Chrono (chemo) therapy?

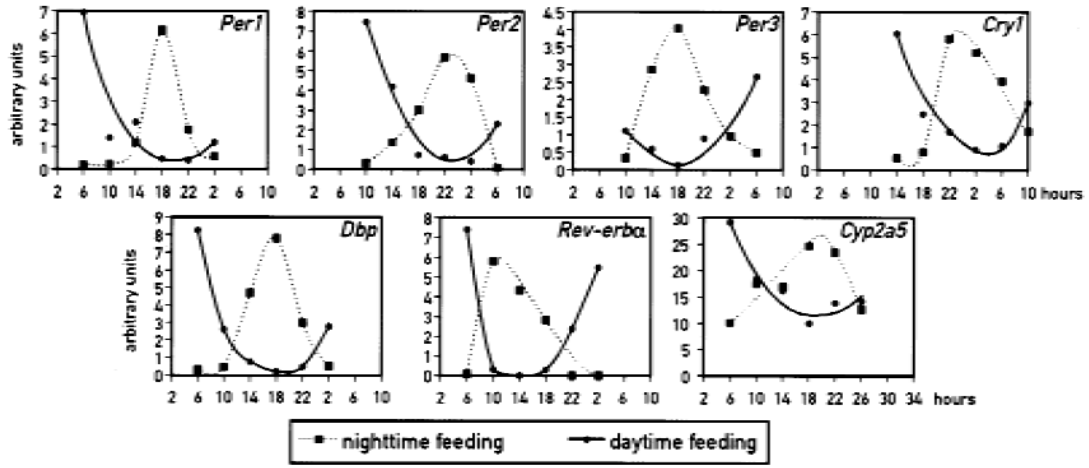
- Chemotherapy at different times of day: Does it make a (big) difference?
- Inhibition/activation of circadian timekeeping in a tumor?
- Gliobastomas.

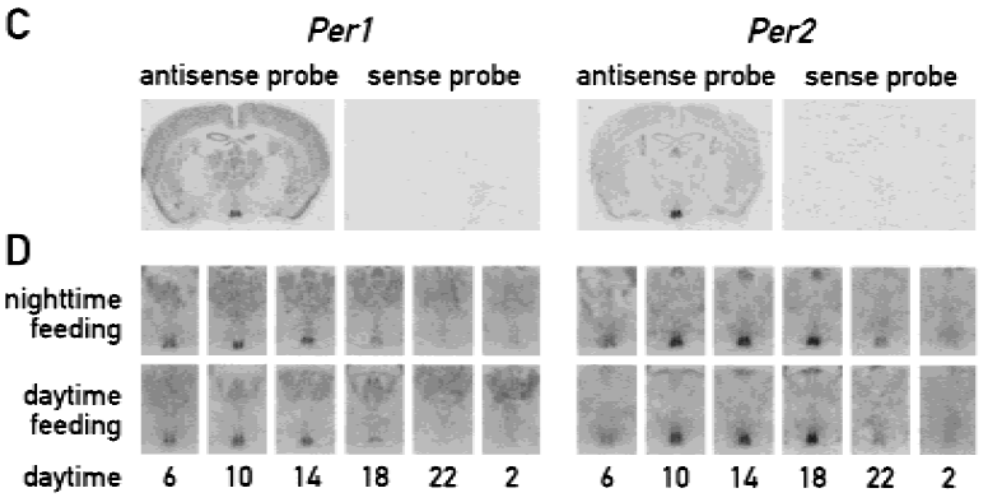
Timing of food intake and metabolism

Food/metabolic effects: Daytime vs nighttime feeding has a dramatic effect on the timing of liver circadian gene expression

(this is a peripheral clock; there is no effect on the SCN clock)







Early paper with therapeutic implications well beyond “normal” metabolism

J Neurosci. 2010 Jul 28;30(30):10199-204. doi: 10.1523/JNEUROSCI.1694-10.2010.

Disruption of peripheral circadian timekeeping in a mouse model of Huntington's disease and its restoration by temporally scheduled feeding

Elizabeth S Maywood [1], Eloise Fraenkel, Catherine J McAllister, Nigel Wood, Akhilesh B Reddy, Michael H Hastings, A Jennifer Morton

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

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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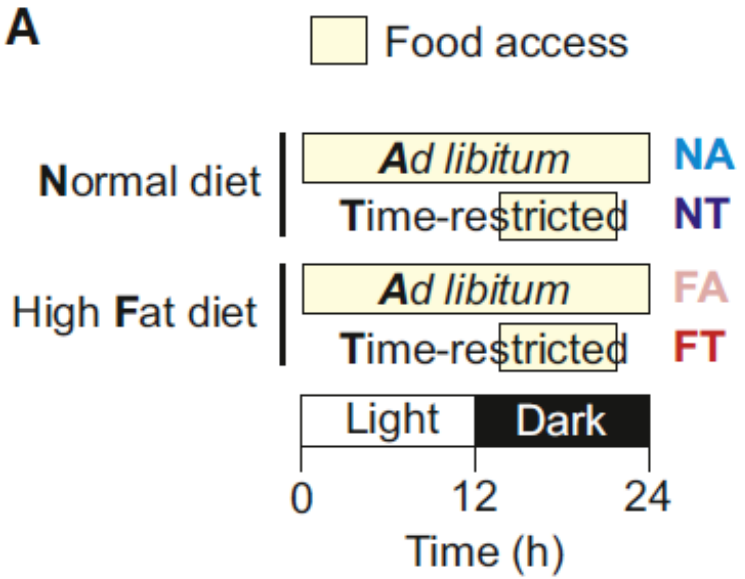
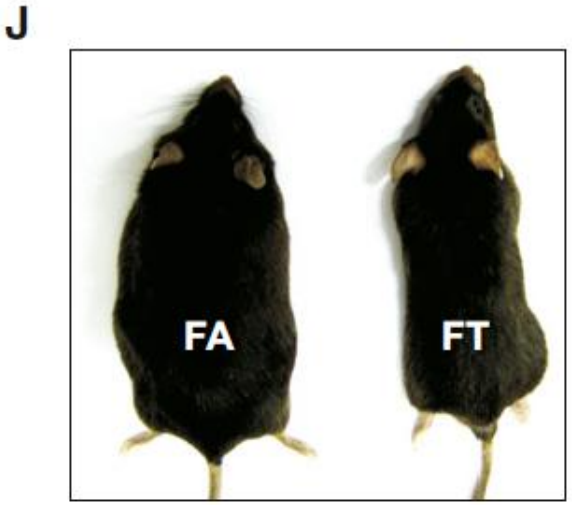
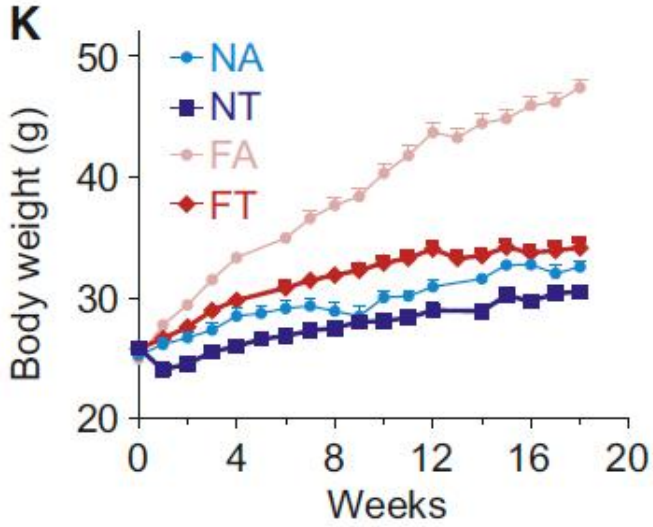
DOI 10.1016/j.cmet.2012.04.019







Hatori et al. Cell Metab 3:e04617, 2014

Humans: TRE

Received: 1 July 2022 | Revised: 27 September 2022 | Accepted: 4 October 2022

DOI: 10.1002/oby.23614

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Time-Restricted Eating

Early time-restricted eating affects weight, metabolic health, mood, and sleep in adherent completers: A secondary analysis

Felicia L. Steger[1,2] | Humaira Jamshed[1,3] | David R. Bryan[1] | Joshua S. Richman[4] | Amy H. Warriner[5] | Cody J. Hanick[1] | Corby K. Martin[6] | Sarah-Jeanne Salvy[7] | Courtney M. Peterson[1]

[1]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA

JCI The Journal of Clinical Investigation

Daytime-restricted parenteral feeding is associated with earlier oral intake in children following stem cell transplant

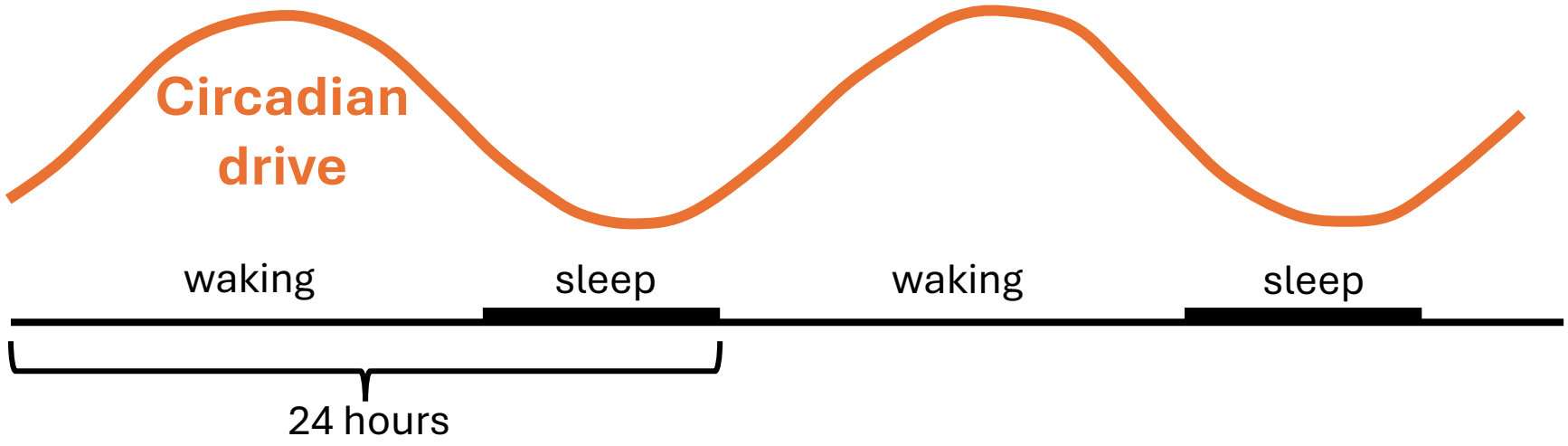
YunZu Michele Wang, … , John B. Hogenesch, Christopher E. Dandoy

J Clin Invest. 2023;133(4):e167275. https://doi.org/10.1172/JCI167275.

Another challenge: understanding the basic science of sleep and improving human health

Narcolepsy and Orexin

We understand quite a bit about the circadian control of sleep



Based on Borbély, 1982

Human mendelian mutants/variants of four *Drosophila* clock genes cause human sleep syndromes

(ASPS/ DSPS; Mendelian extreme chronotype disorders)

	Clock*	⟶	***Doubletime (cKI)****
	Cycle*		***Shaggy (GSK3)****
⟶	***Period ****		***cKII****
	Timeless		***Nemo***
⟶	***Cry (*)***		***PP2A****
	Vrille*		***PP1****
	Pdp1*		
⟶	***Cwo****		

Early Birds, Night Owls and Chronotype

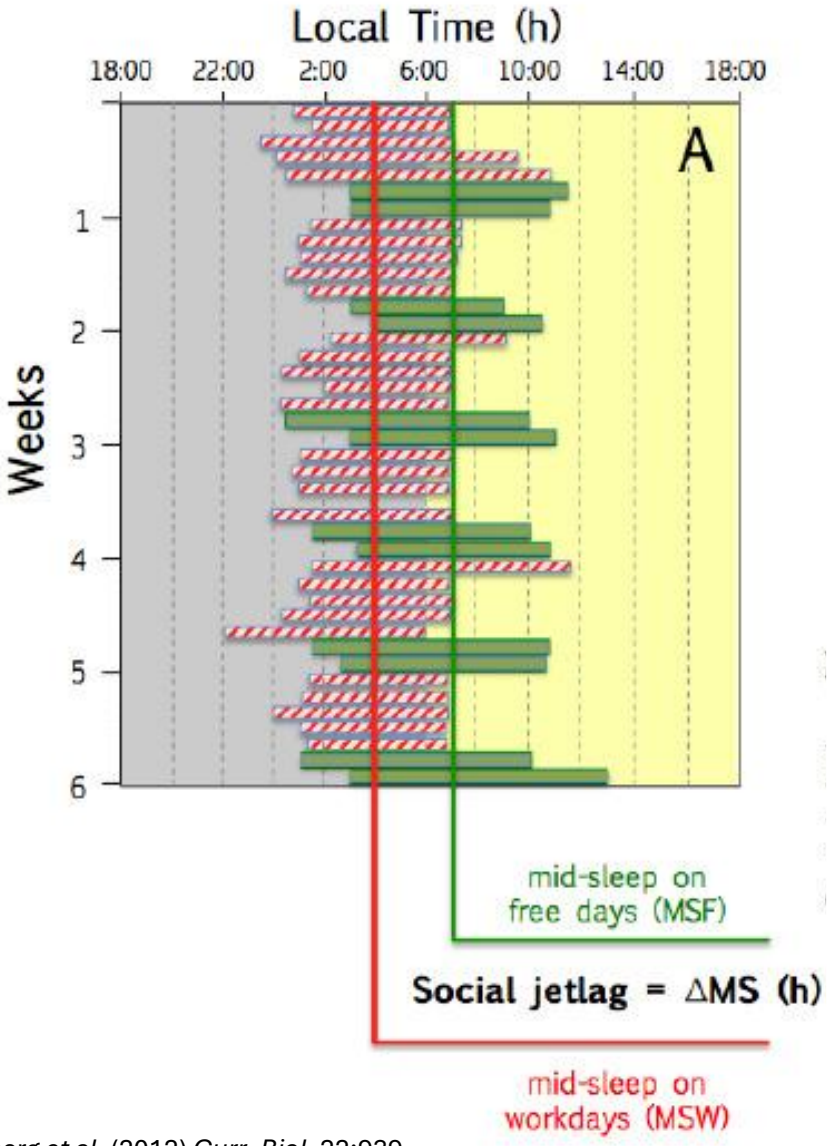
Chronotype is heritable and clock genes contribute to this phenotype

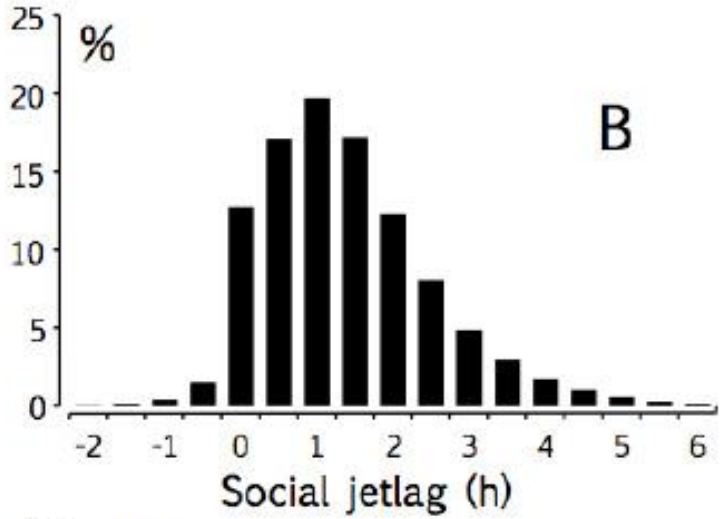
Table 3 Pairwise polychoric correlations (and no. pairs) for diurnal type (including four categories) among twin pairs by zygosity, age and sex

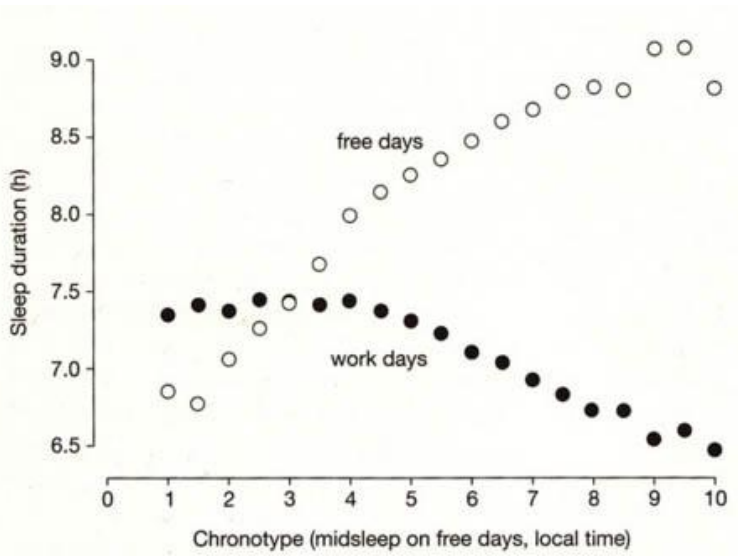
	Monozygotic	*Dizygotic*
Males aged		
24–34	0.467 (572)	0.087 (1296)
35–49	0.490 (420)	0.185 (979)
50 and older	0.288 (237)	0.120 (492)
All	0.472 (1229)	0.182 (2767)
Females aged		
24–34	0.458 (774)	0.136 (1452)
35–49	0.538 (495)	0.052 (1013)
50 and older	0.501 (338)	0.064 (685)
All	0.516 (1607)	0.128 (3150)
All subjects aged		
24–34	0.461 (1346)	0.115 (2748)
35–49	0.513 (915)	0.116 (1992)
50 and older	0.412 (575)	0.087 (1177)
All	0.497 (2836)	0.153 (5917)

Koskenvuo *et al.* (2007) *J. Sleep. Res.*. **16:** 156

Social Jet Lag (SJL) of an owl (>> early birds)



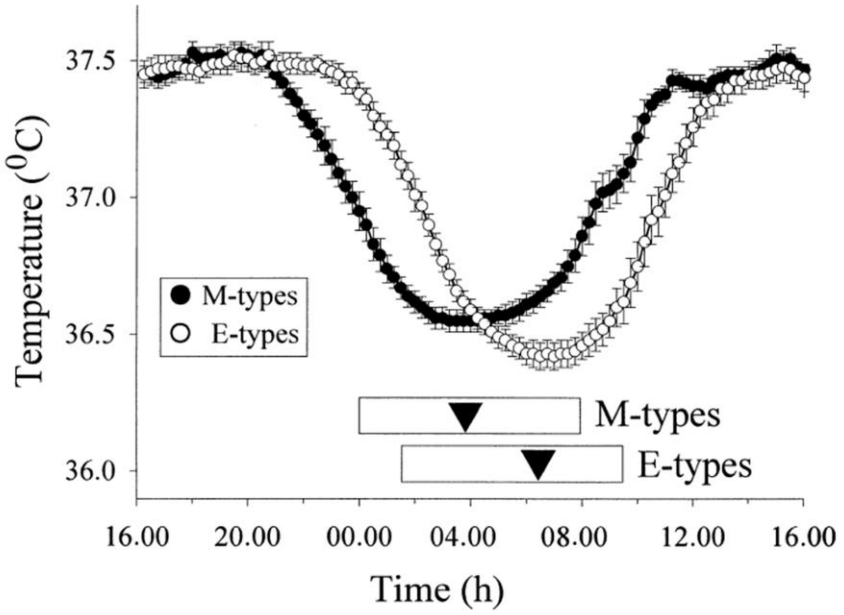


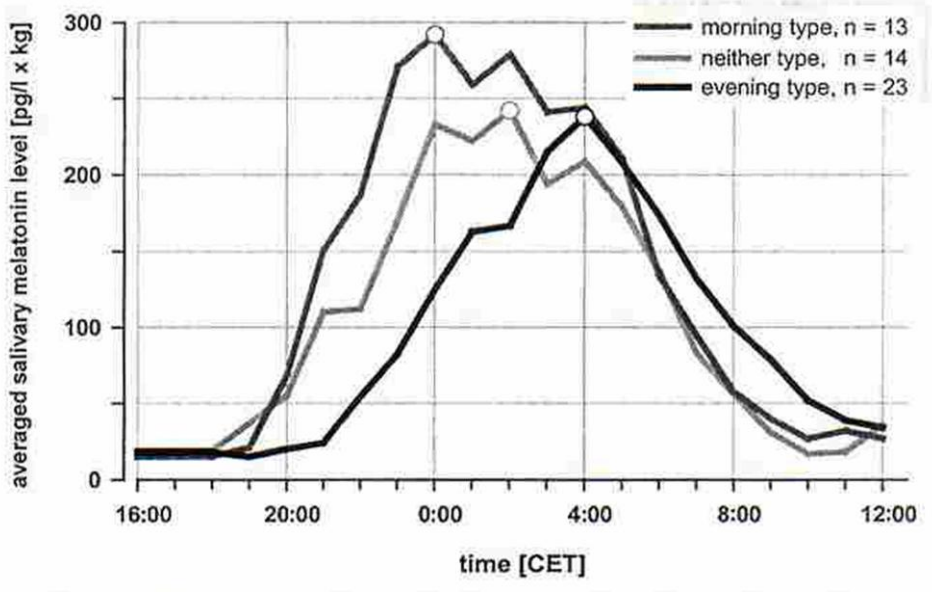


Roenneberg *et al.* (2012) *Curr. Biol.* 22:939

Roenneberg *"Internal Time"*

Body Temperature and salivary melatonin rhythms are phased advanced in Horne-Östberg morning-types.

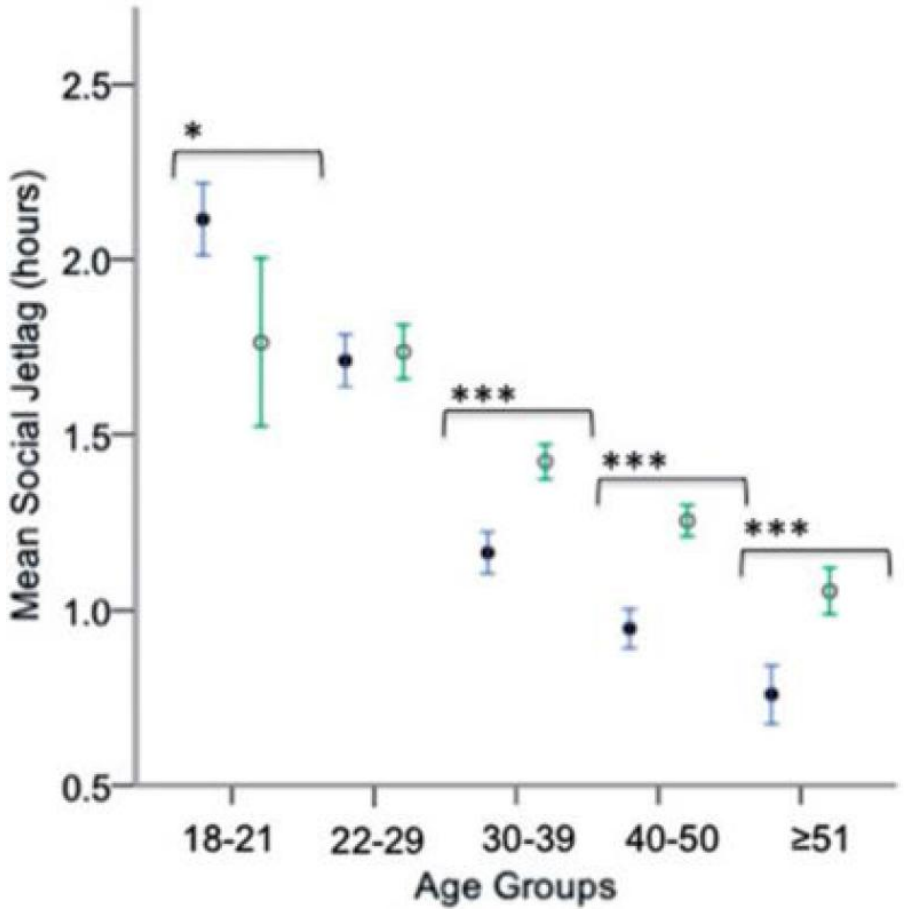




Baehr *et al.* (2000) *J. Sleep. Res.* **9:**117

Griefan *et al.* (2003) *Mil. Med.*. ***168*:** 674

Young people have much later chronotypes (owl-like) than adults: implications for school start time



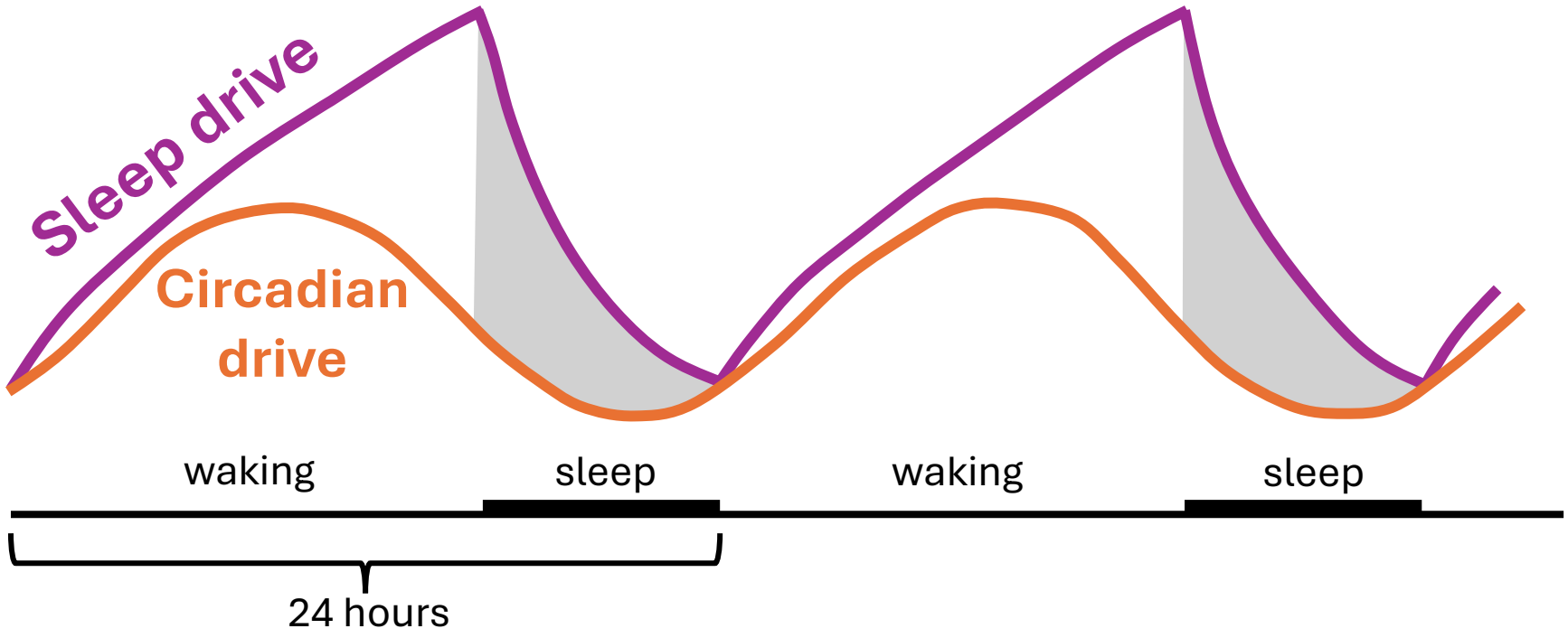
Daytime (morning) light is good

whereas

nighttime (evening) light is bad

- Western and eastern edges of time zones
- DST vs standard time
- Illuminating the earth at night from satellites: Reflect Orbital and SpaceX

We understand much less about the homeostatic control of sleep (sleep drive here)



Based on Borbély, 1982

Sleep homeostasis or sleep drive

- Where/What is keeping track of sleep need?

- Why do we sleep? What is the conserved function(s) of sleep.

Humans

- People are very excited about short sleepers (families): They may be long-lived and resilient

Flies really sleep like we do. Might they illuminate how and why we sleep?

A period of quiescence associated with a species specific posture

An increase in arousal threshold

Quick reversibility to wakefulness

Interactions with the circadian clock

Conserved signaling pathways
Conserved function of neurotransmitters
Conserved effects of hypnotic/stimulant drugs

Homeostasis

Young flies sleep much more than mature flies

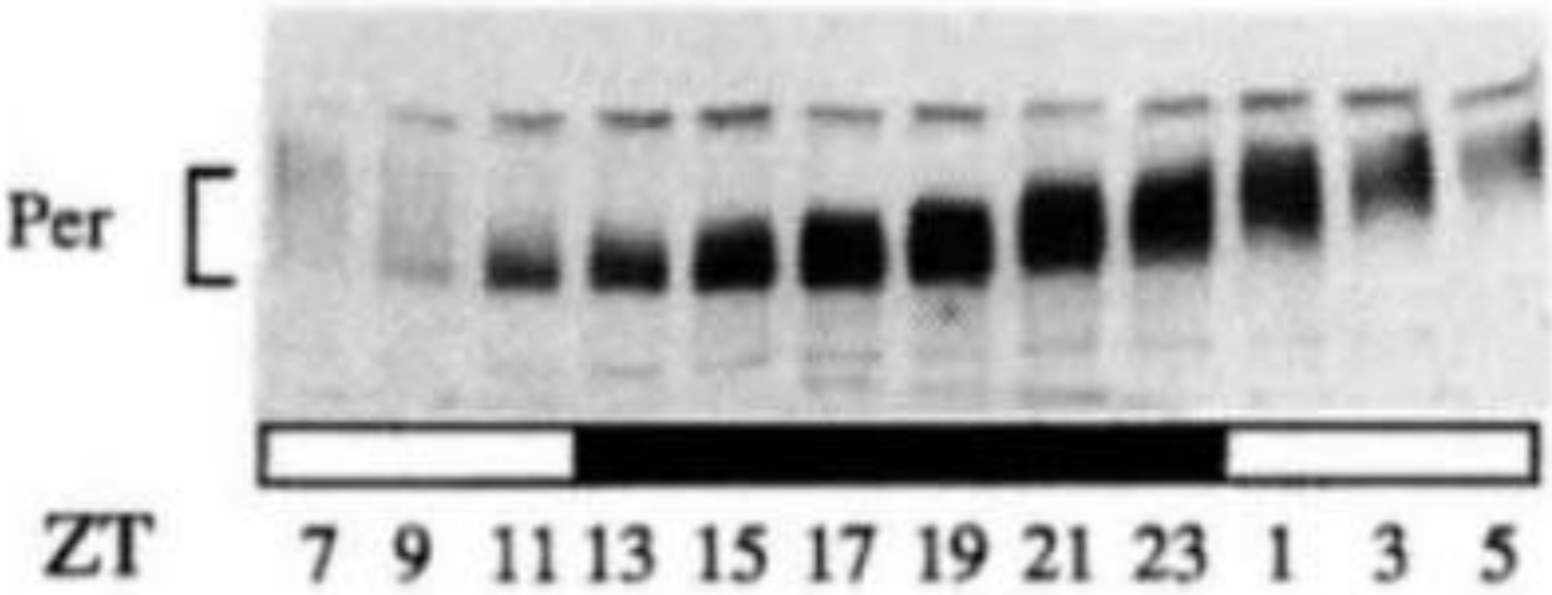
Aging causes sleep fragmentation!

A third challenge to the future and the importance of biochemistry and structural biology:

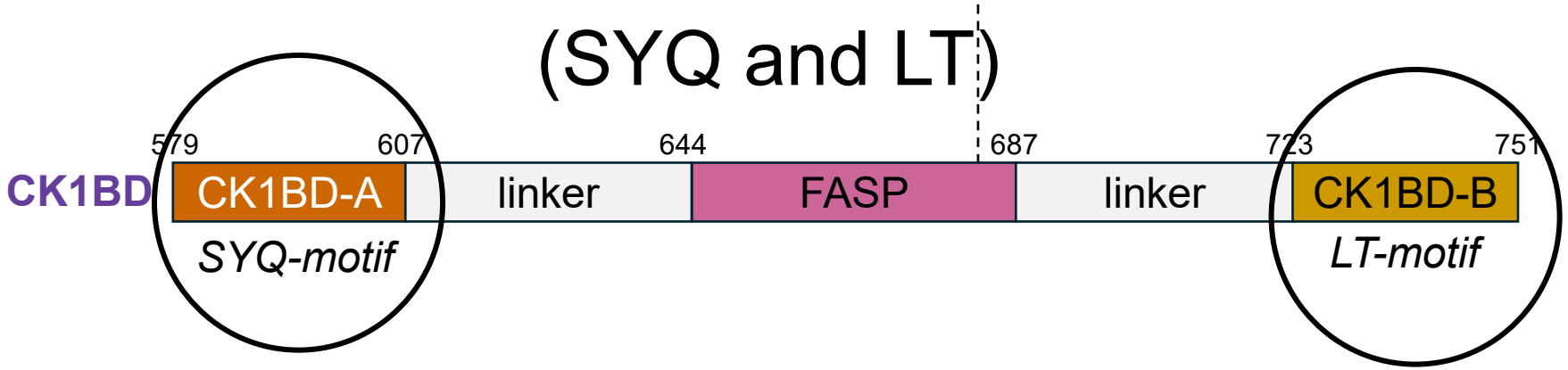
What determines the circadian period, e.g., why 24.2 hrs for humans?

Why is circadian timekeeping temperature-independent, with a Q10 ≅1.0?

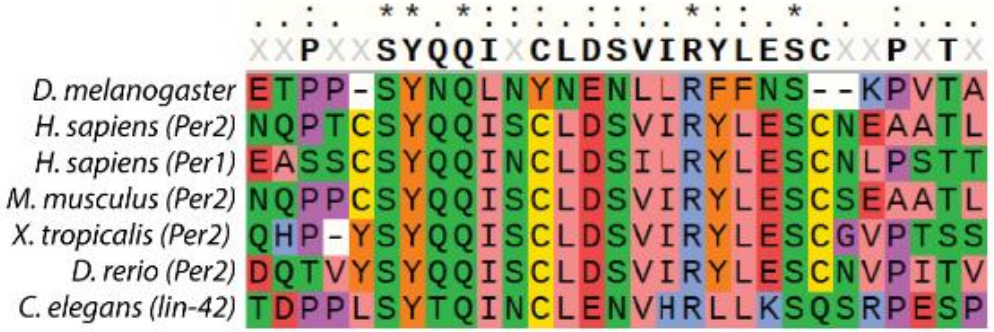
The clock protein PER undergoes slow and massive phosphorylation by CK1/DBT over many hours before undergoing degradation, in mammals as well as in flies



Although PER is mostly unstructured, there is a key CK1/DBT interacting region of PER that contains two highly conserved alpha helices

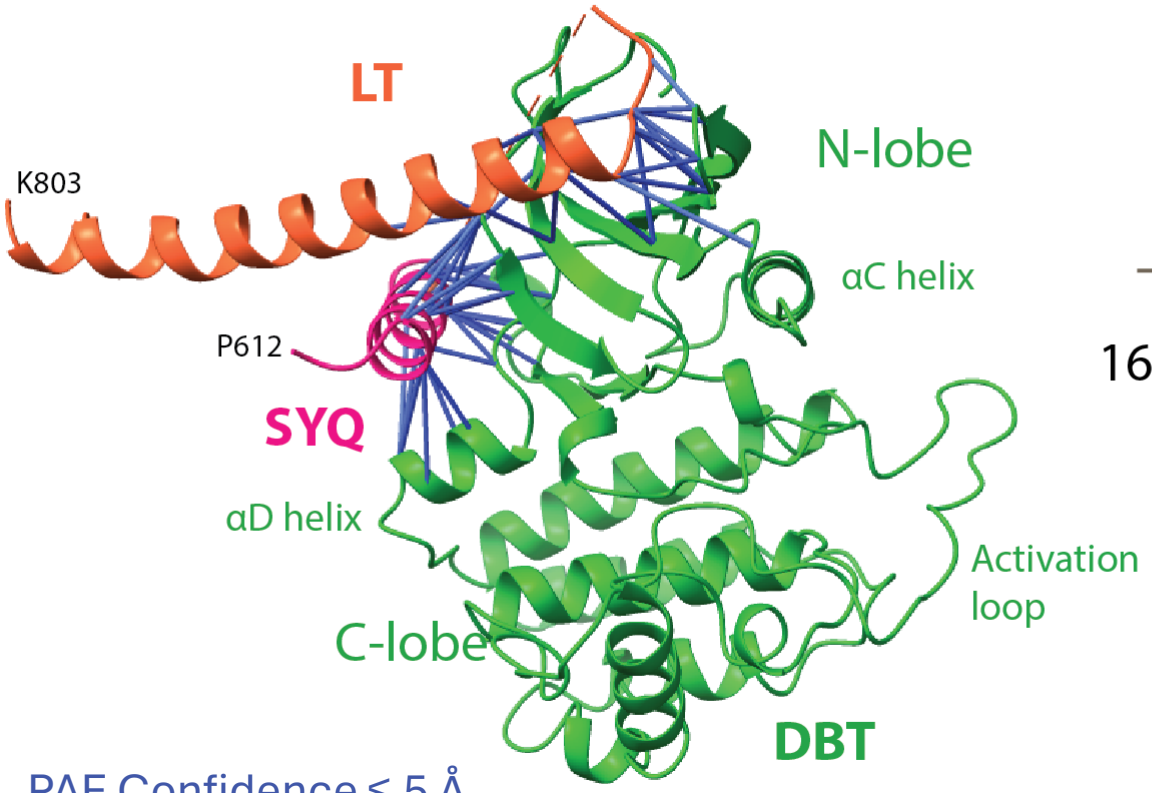


SYQ Domain

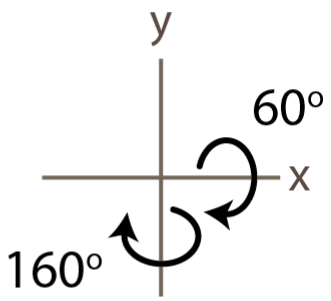


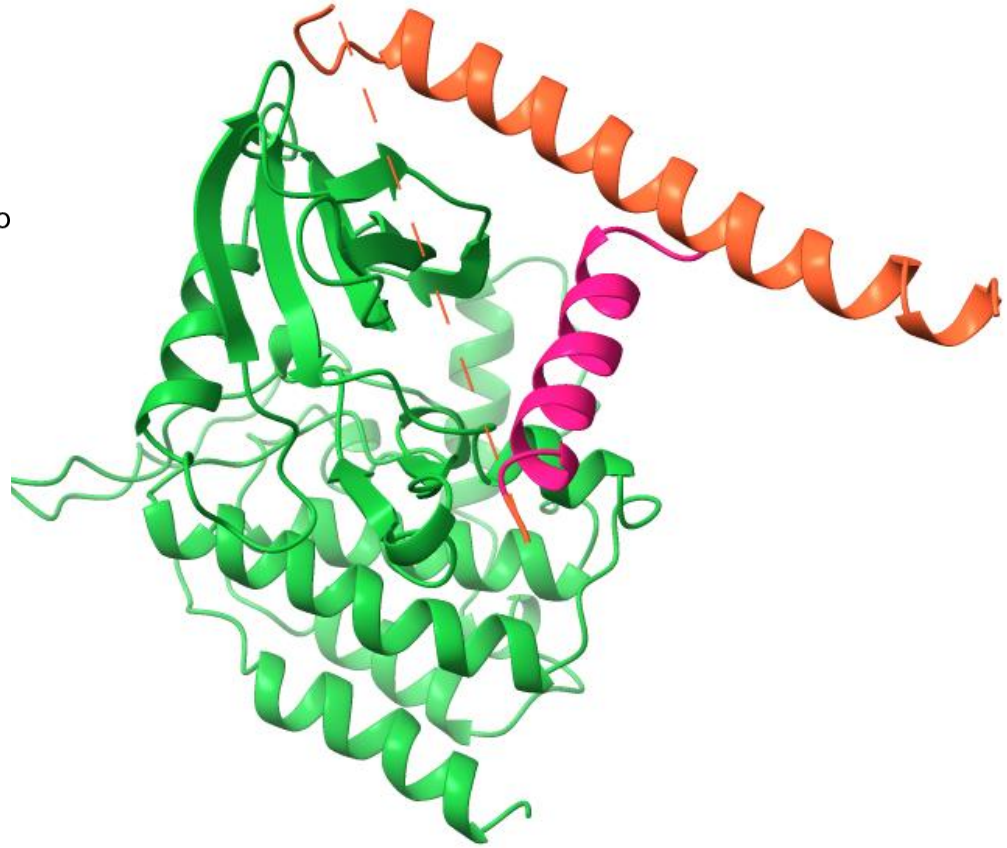
LT Domain

AlphaFold predicts a high confidence interaction between the PER SYQ and LT alpha helices and Doubletime/CK1



PAE Confidence ≤ 5 Å

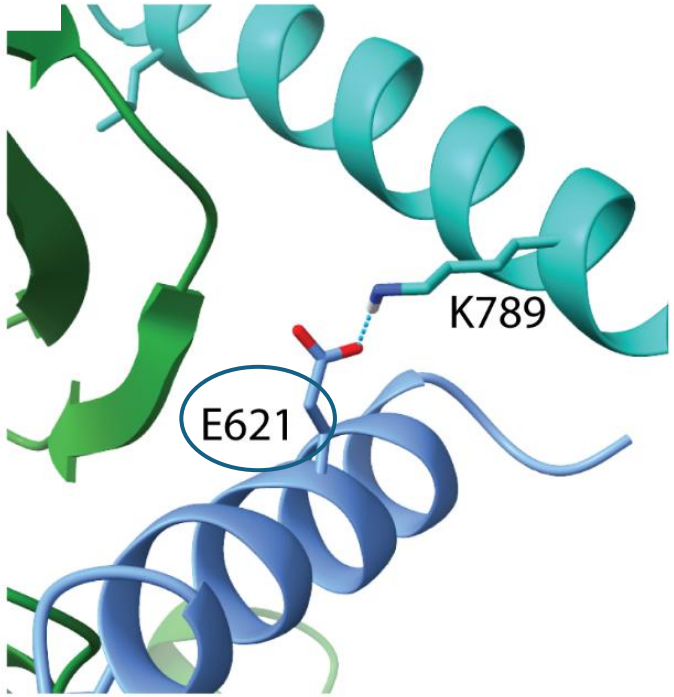


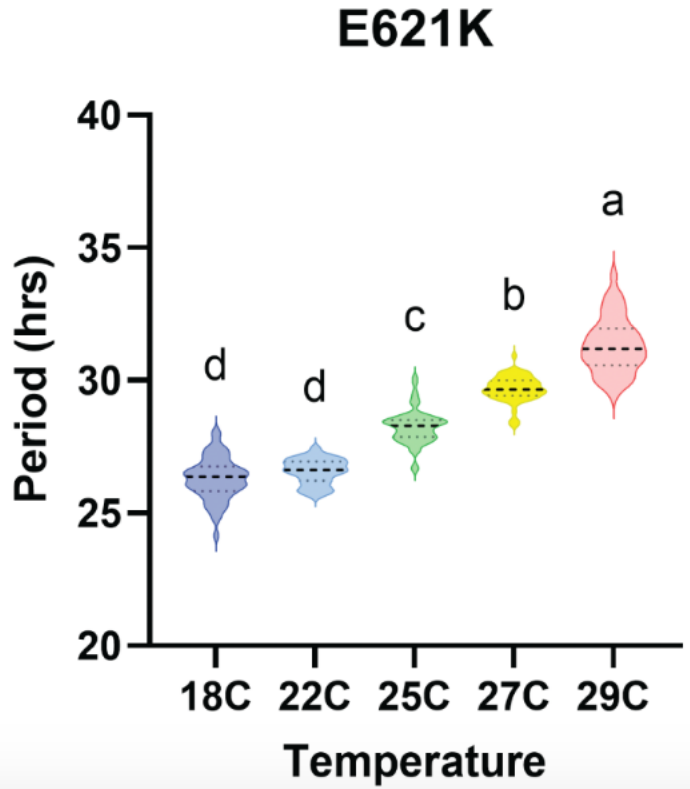


Make mutations based on predicted structure and then assay them phenotypically in the fly

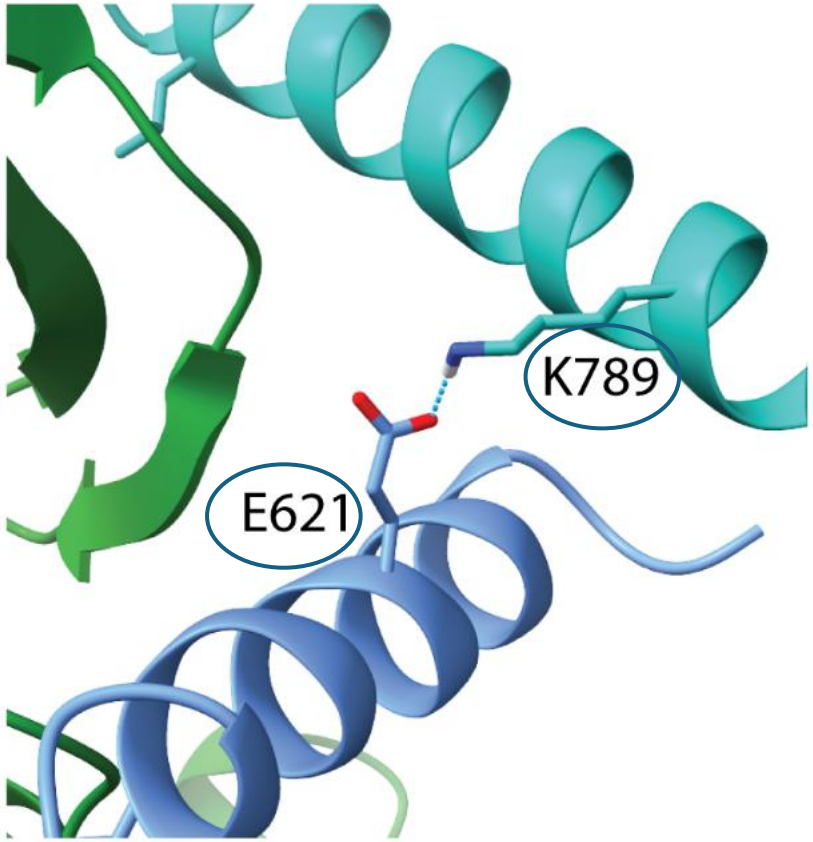
One example: Disrupting the predicted structure, mutating a highly conserved salt bridge between SYQ and LT, causes a long period and profound temp-sensitivity

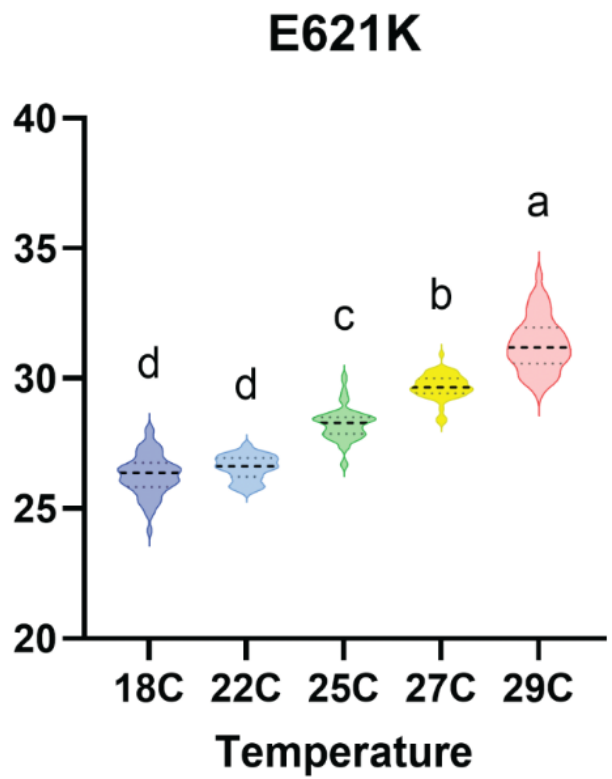
E621K, K-K instead of E-K

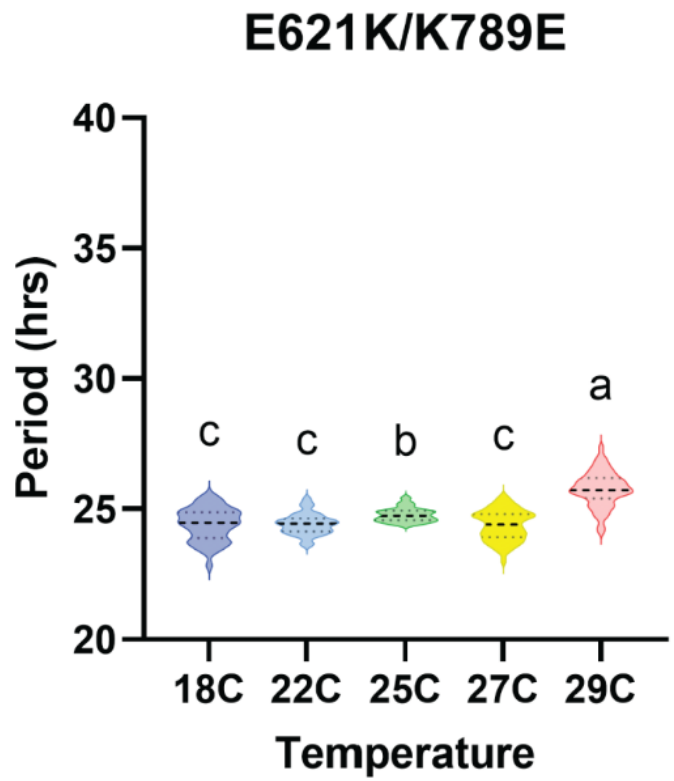




A double mutant charge swap that recreates the salt bridge rescues the period effect and restores temperature-independence!!

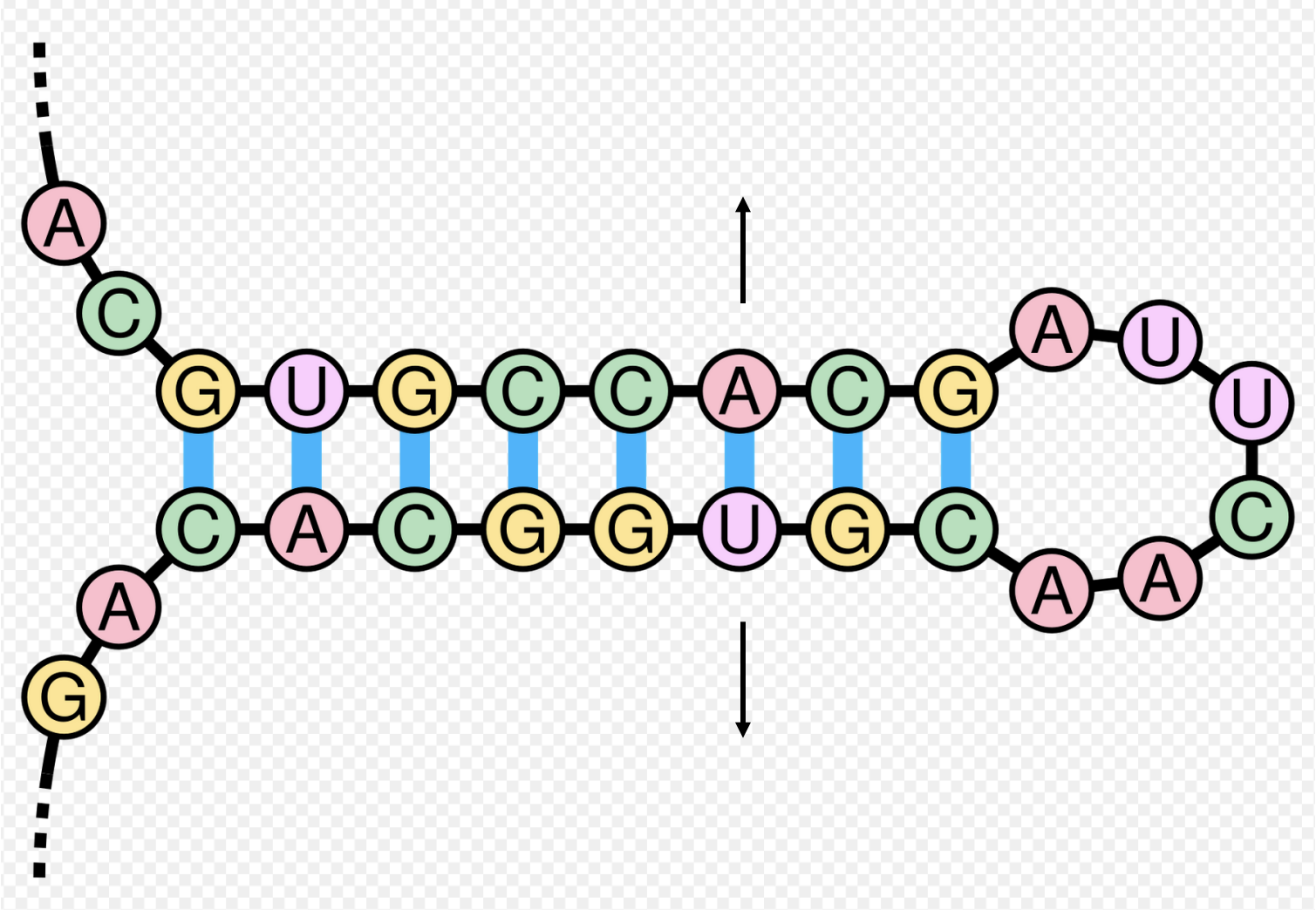






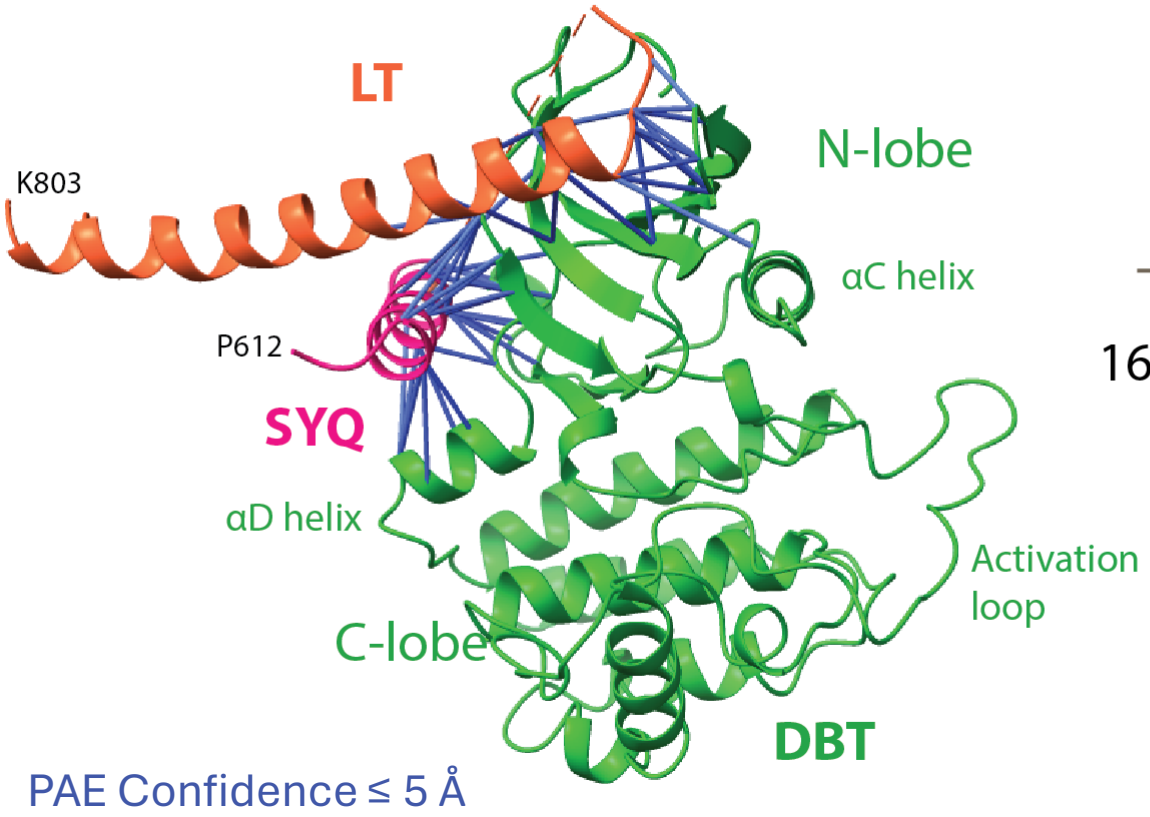
Biochemical assays as well

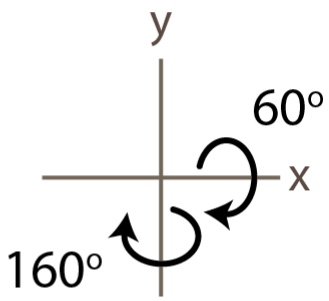
A la recherche du temps perdu: RNA helices

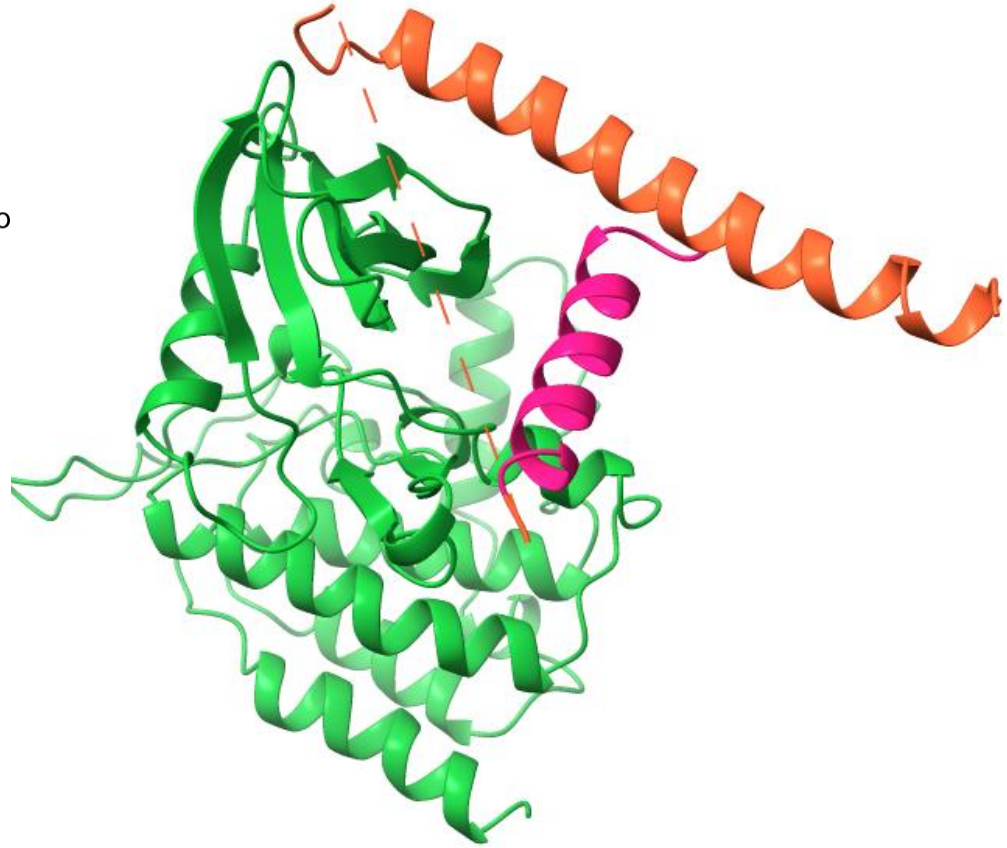


This structure may contribute to the temperature-insensitivity (Q10 ≅1.0) of circadian timing

AlphaFold has had and continues to have a massive influence on Biology and Biochemistry, which has fueled confidence in (and investment in) in AI







Importantly, AlphaFold was/is 100% dependent on the PDB

- **As of early 2026, the PDB contains approximately 240,000 experimentally determined structures**, accumulated over roughly **55 years** — the database was founded in **1971** with just 7 structures.

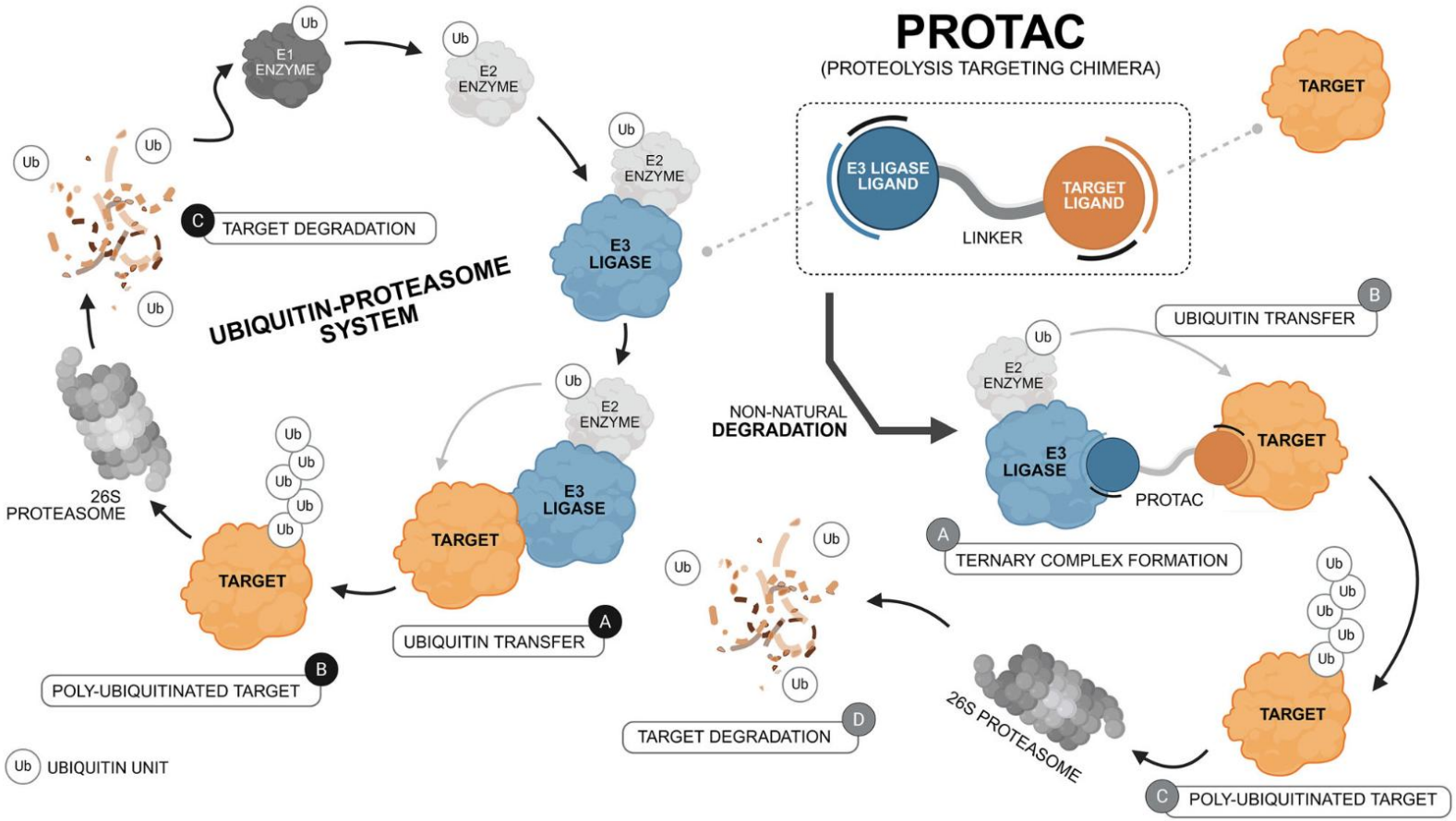
- (Data from Claude)

Essentially 100% of druggable proteins have orthostatic pockets

- They or family members bind ligands, prosthetic groups etc.

- Circadian example: Attempts to make a jet lag or phase shift drug are all exploiting this traditional principle (Bmal1, Rev-erb etc.)

PROTAC: Bifunctional molecules that degrade the target protein

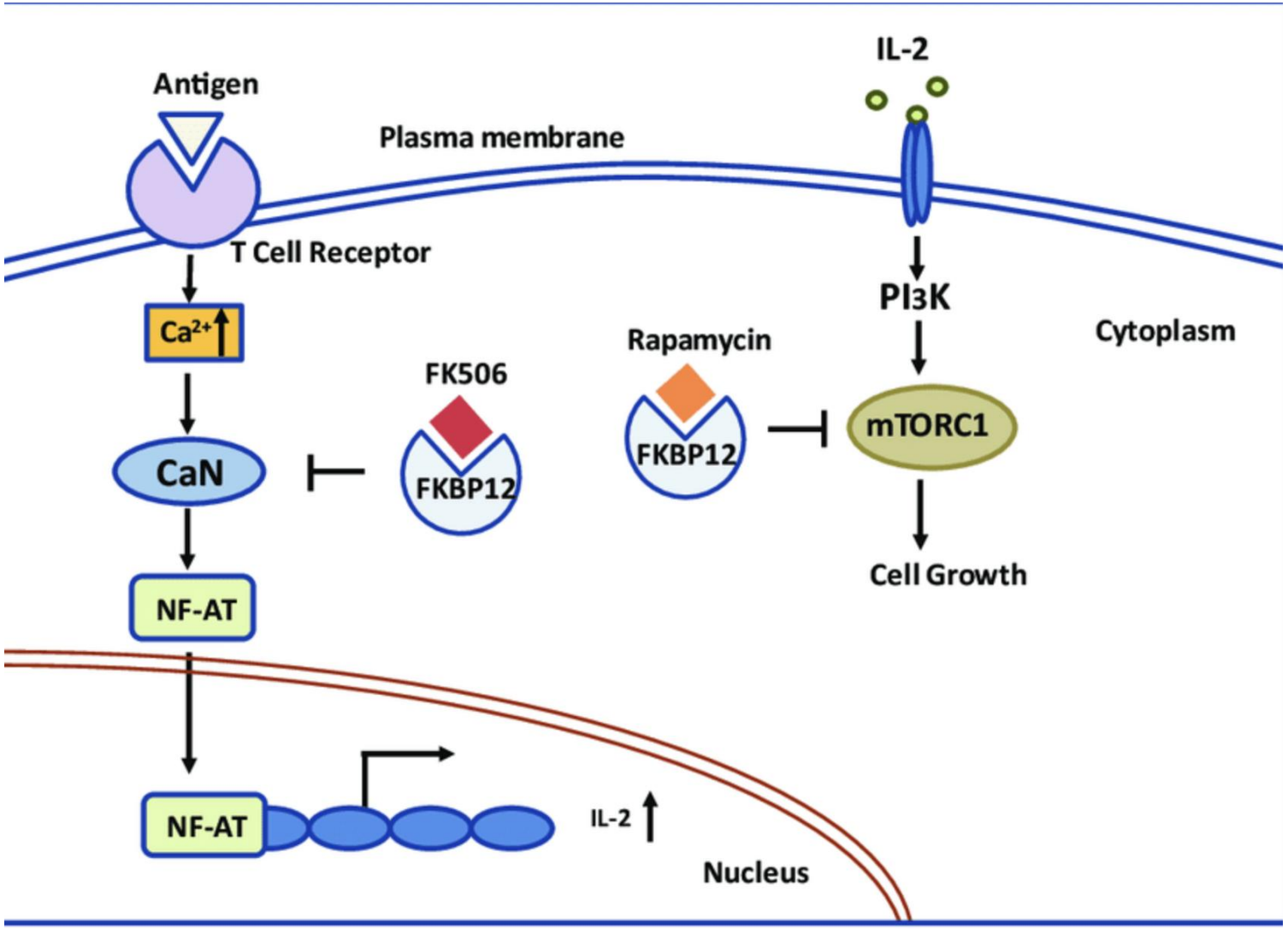


There is no comparable strategy for undruggable proteins

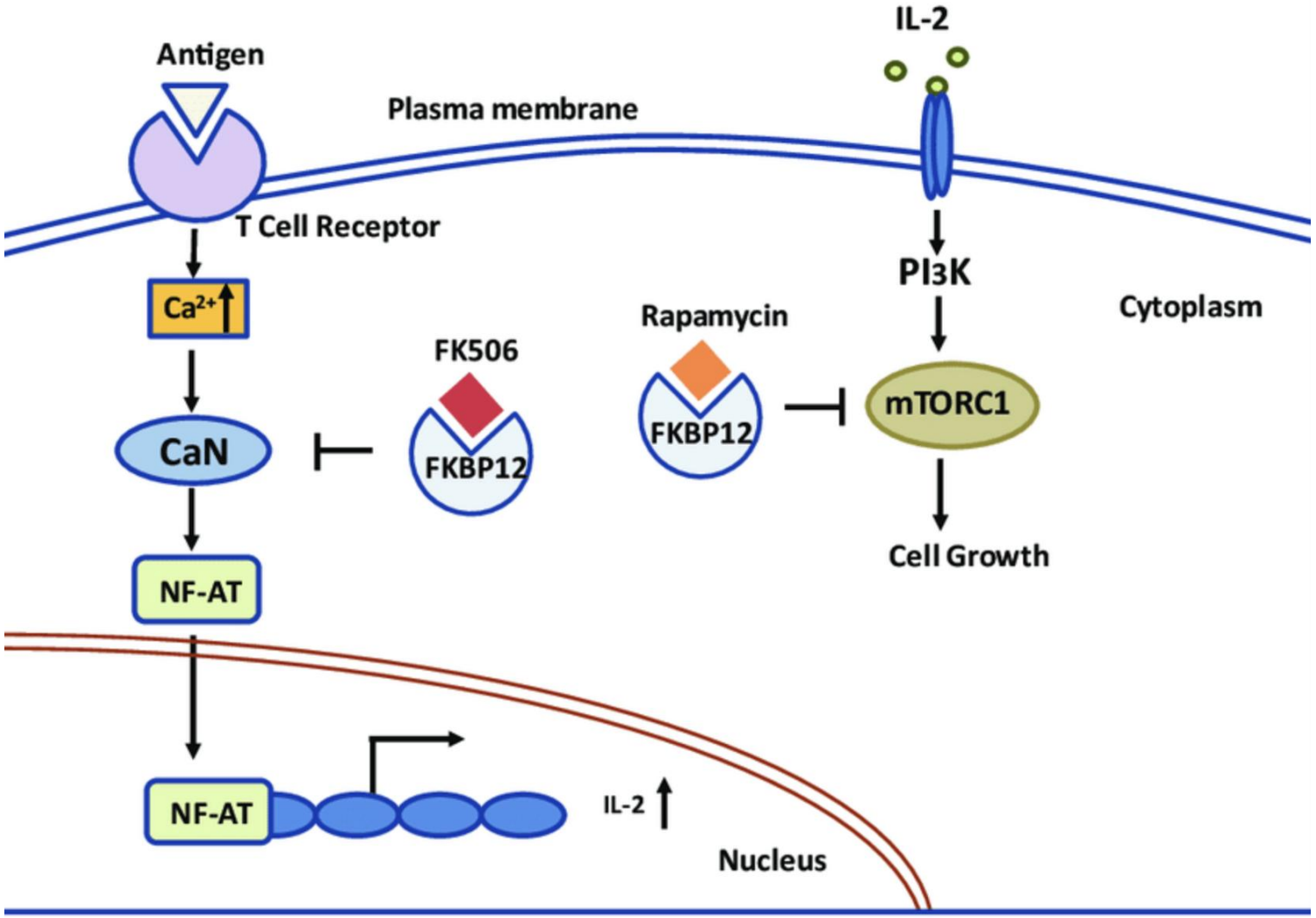
- Meaning there is no massive database that can help us predict which synthesized chemicals can act as drugs with important therapeutic properties by binding to “undruggable” proteins.

- The following is a lesson I learned from Magnet Biomedicine.

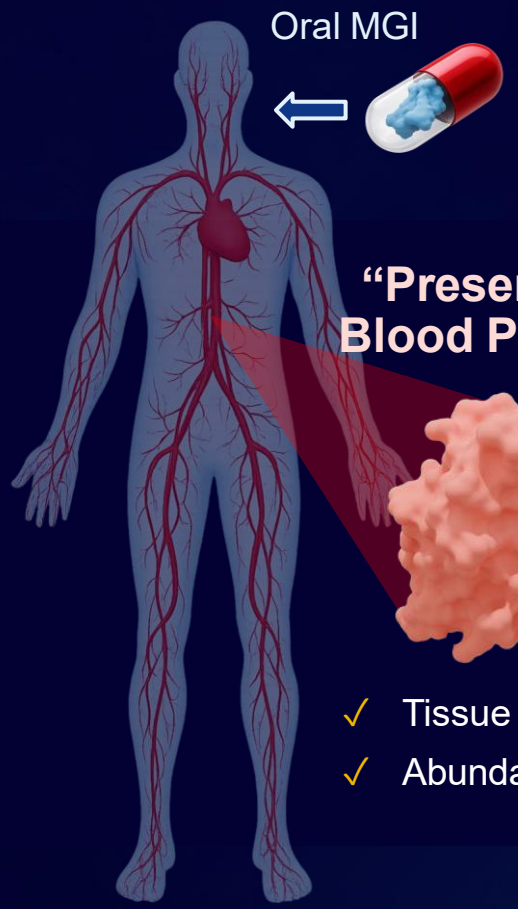
What is a molecular glue?
An artificial FK506 or Rapamycin



Challenge: Find a high concentration super-presenter like FKBP12 in serum to enable the inhibition of pathogenic extracellular receptors comparable to antibodies.



Magnet Biomedicine: Molecular Glue Inhibitor (MGI)?



*A small molecule that induces an interaction between two proteins that do **not** normally interact.*

"Presenter" Blood Protein

- ✓ Tissue specific
- ✓ Abundant

Presenter-Glue Binary PPI

- ✓ Conformational □
- ✓ Neo-PPI

Pathogenic protein targets

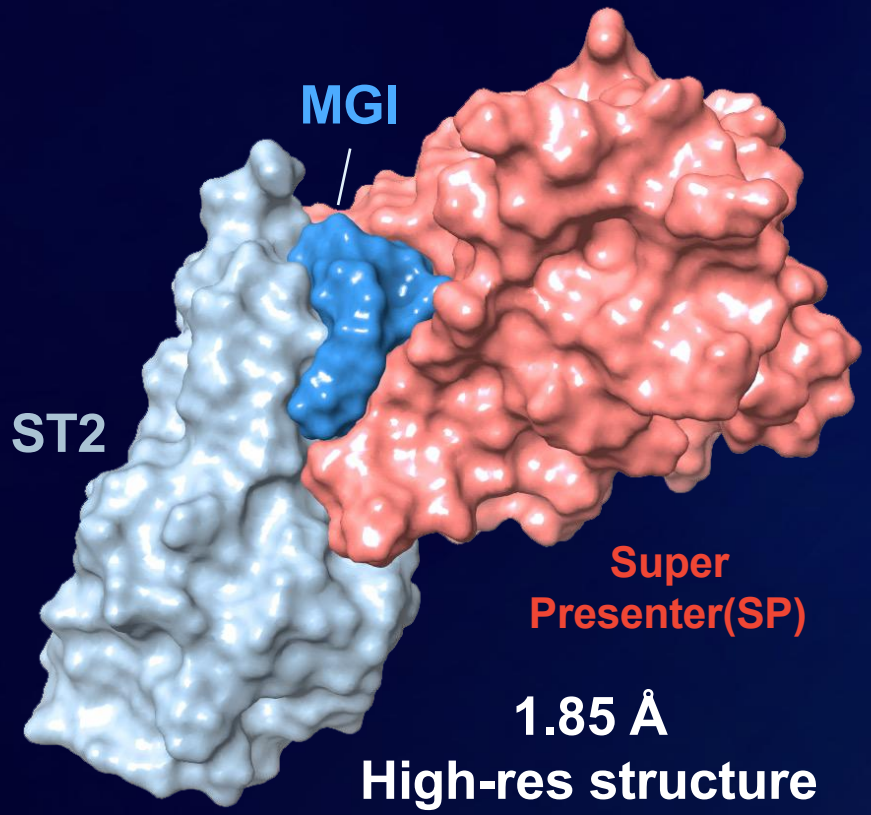
- ✓ Hard-to-drug
- ✓ Highly selective

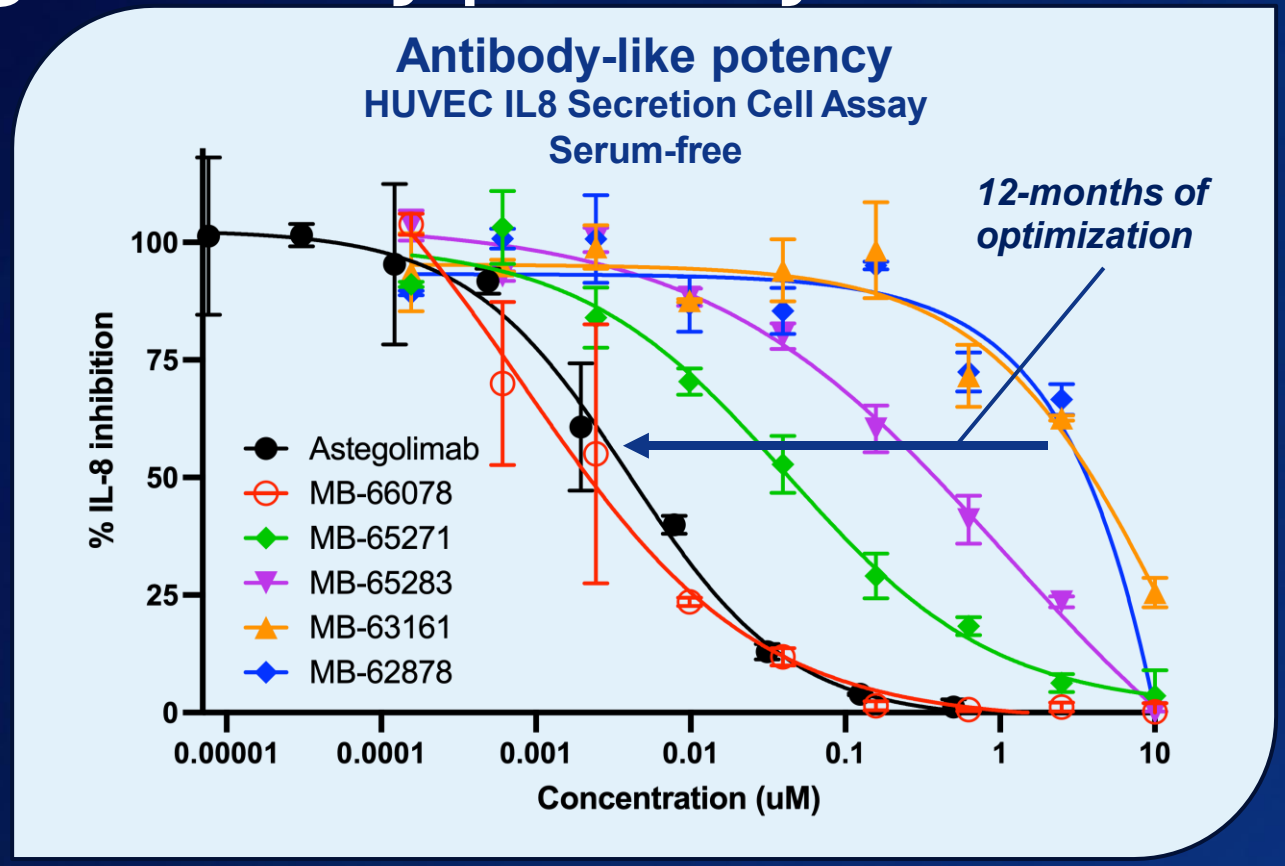
Ternary Complex Blocks Target Protein Function

- ✓ High free drug sink (f_u)
- ✓ Monovalent Molecular Glue Inhibitor

Magnet's TrueGlue™ Platform enables "Oral biologics"

ST2 (IL33 receptor) molecular glue inhibitor (MGI) approaching antibody potency





First-of-its-kind platform delivering antibody-like potency with oral small molecule MGIs; In vivo POC achieved and DC nomination by 4Q26

Key general points from AlphaFold and Rosbash/Magnet experience

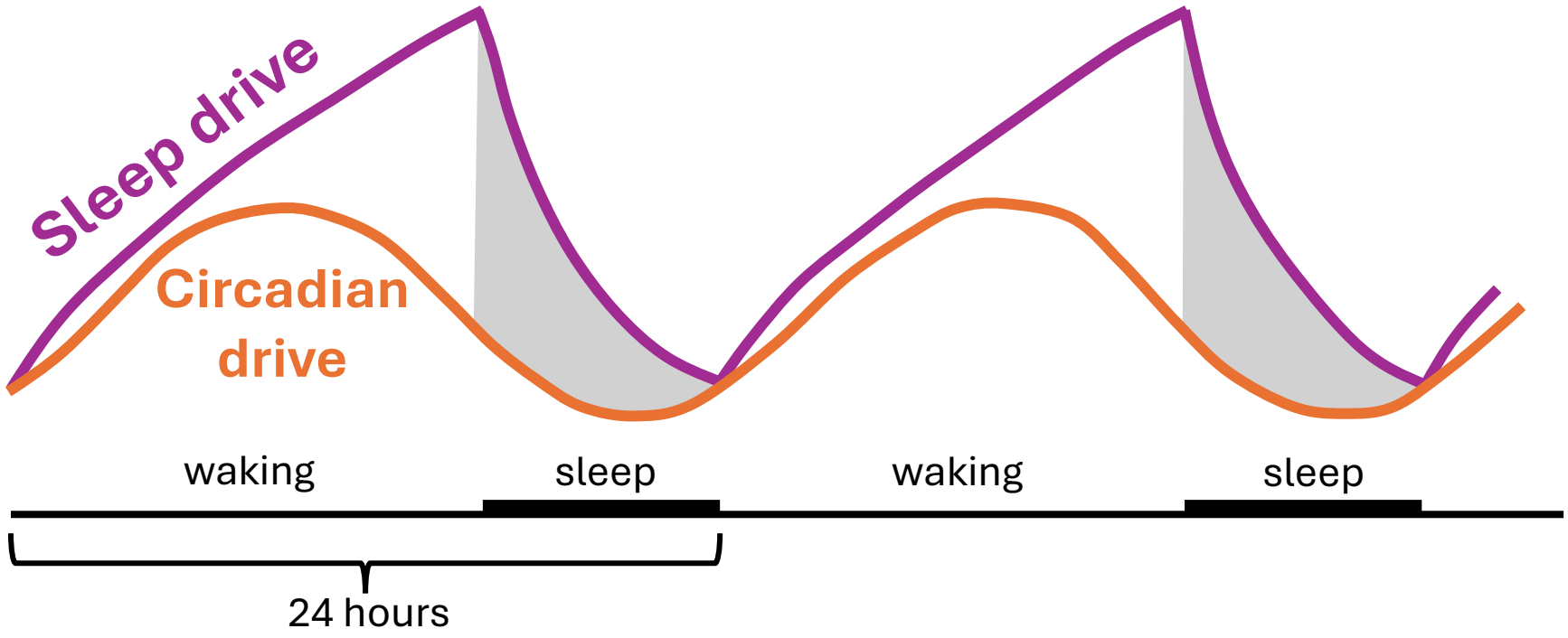
- Despite 3 high resolution crystal structures, computation (viz. AI) could not replace and only barely augments traditional medicinal chemistry optimization.

- To put this most dramatically, chemical binding (or inhibition/activation) cannot be trained on a LLM but needs a database.

- There must be other reasons for this push to replace experimental biology, e.g., animal experiments, with AI.


That's All
Folks!

Another challenge: understanding the basic science of sleep and improving human health



Based on Borbély, 1982

State of the art: the therapeutic anti-ST2 mAb Astegolimab