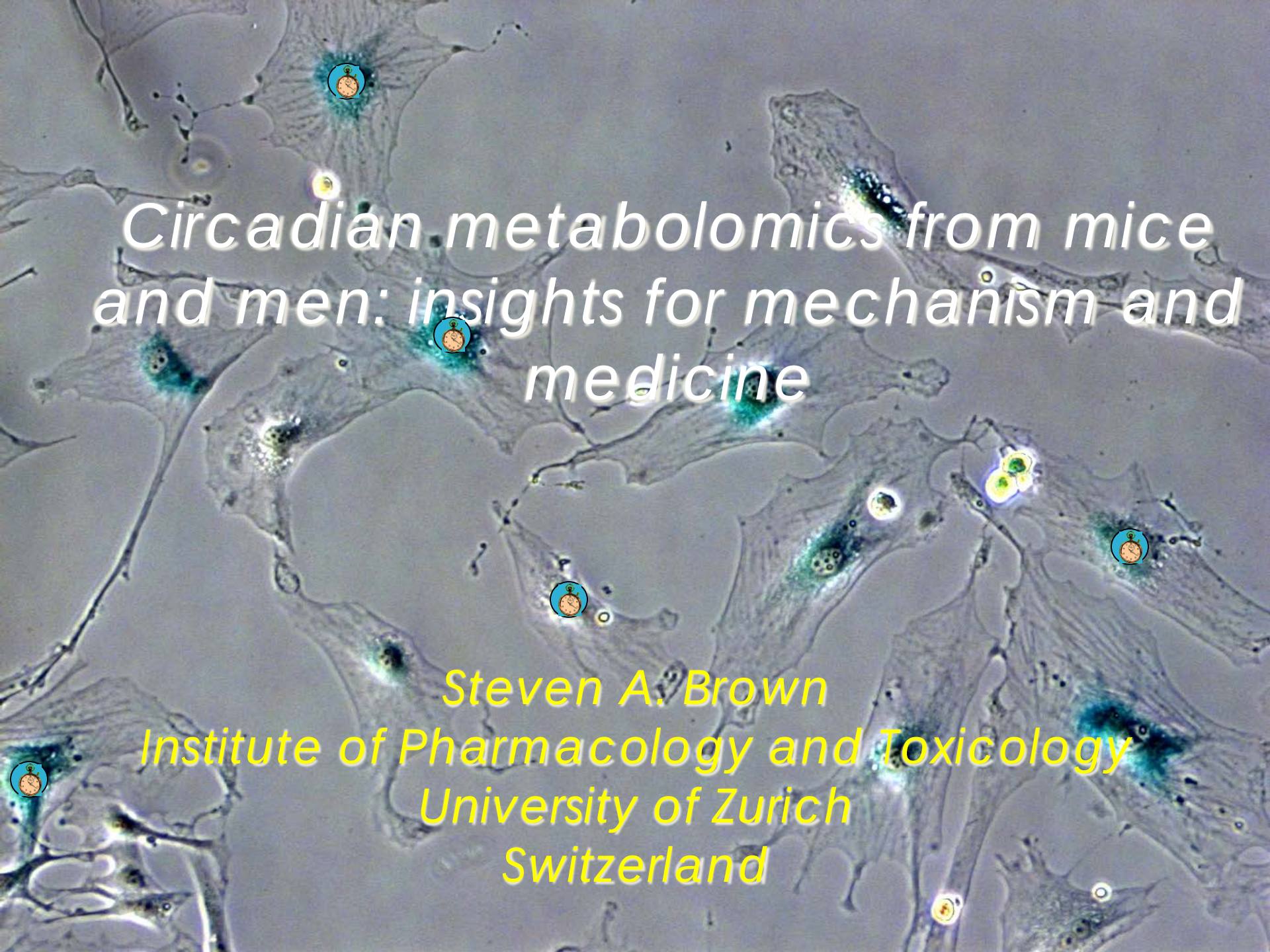


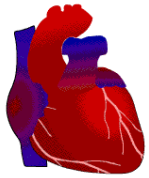
Circadian metabolomics from mice and men: insights for mechanism and medicine

Steven A. Brown
Institute of Pharmacology and Toxicology
University of Zurich
Switzerland

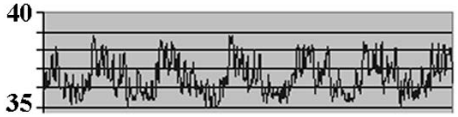
Mammalian physiology is circadian

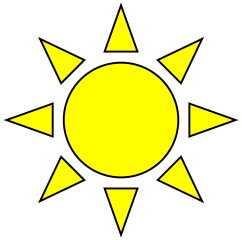
Cardiovascular system: heartbeat, blood pressure

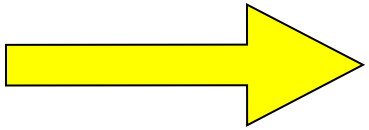
Sleep-wake cycles



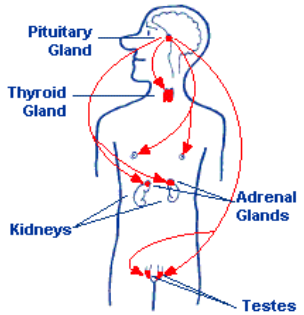
Body temperature





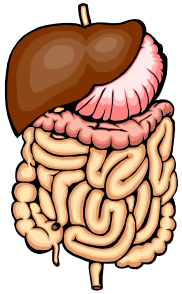


Hormone levels in the blood

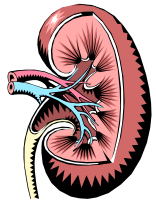


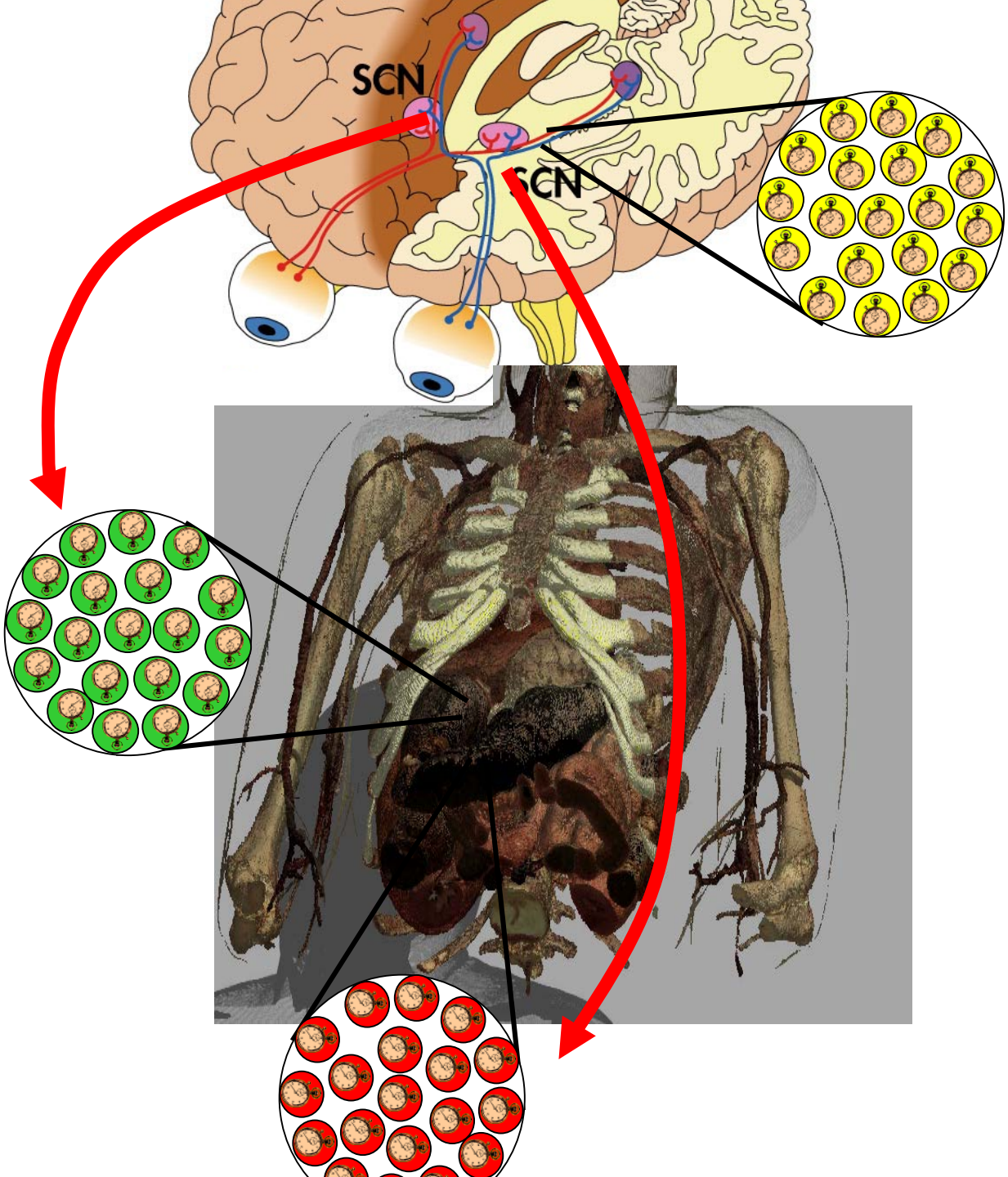
Mating time

Digestion / detoxication



Renal activity




SCN
SCN

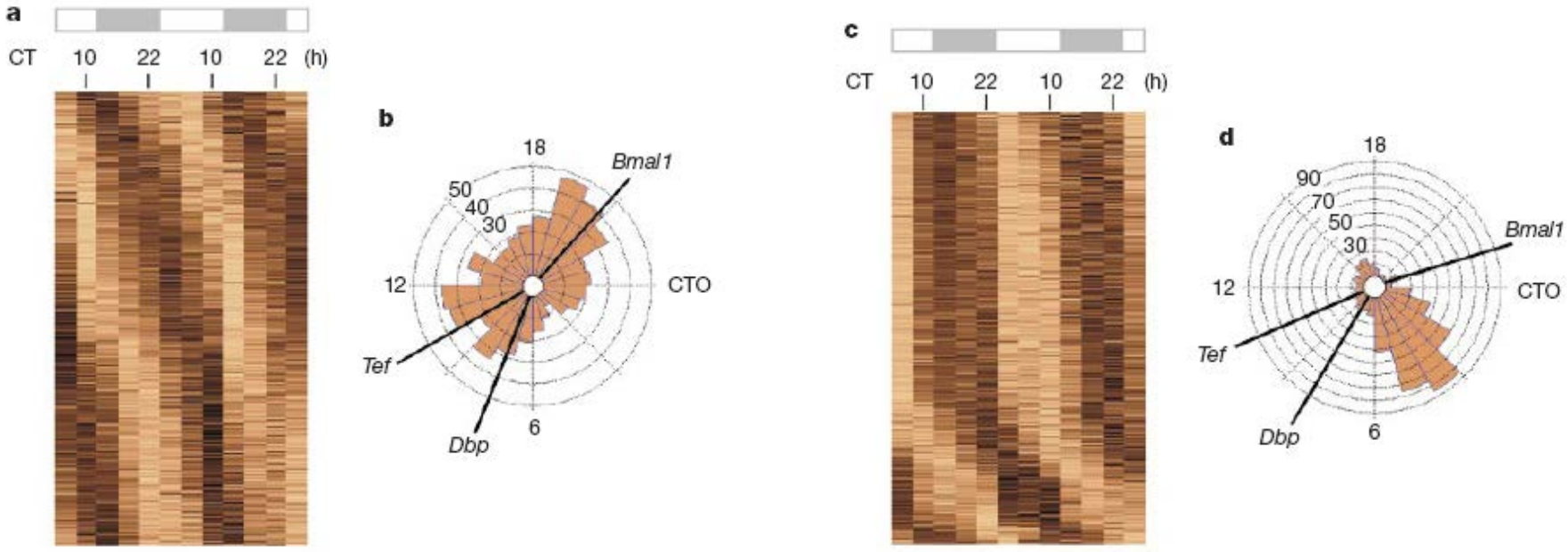
- How do these clocks affect metabolism, and in particular metabolomics?

- What consequences does circadian metabolic control have for cancer?

Ten percent of mouse genes are expressed in circadian fashion

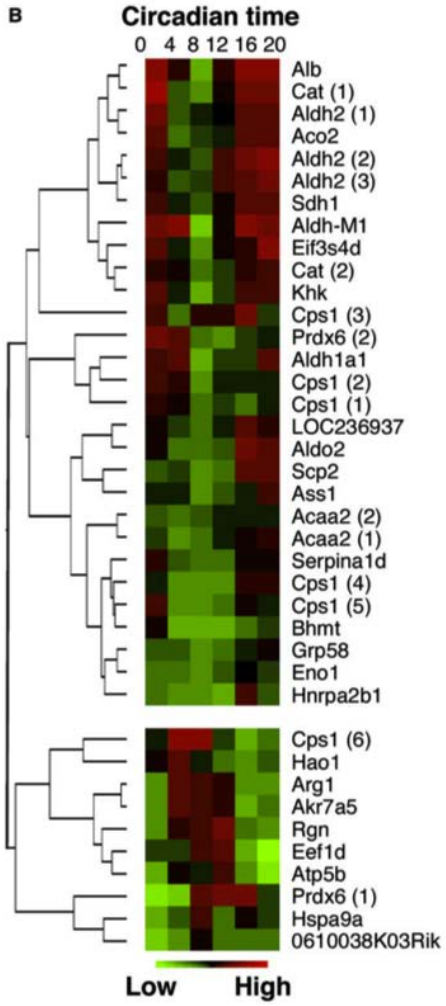
liver

heart



(from Storch et al., 2002)

20% of mouse liver proteins are rhythmic



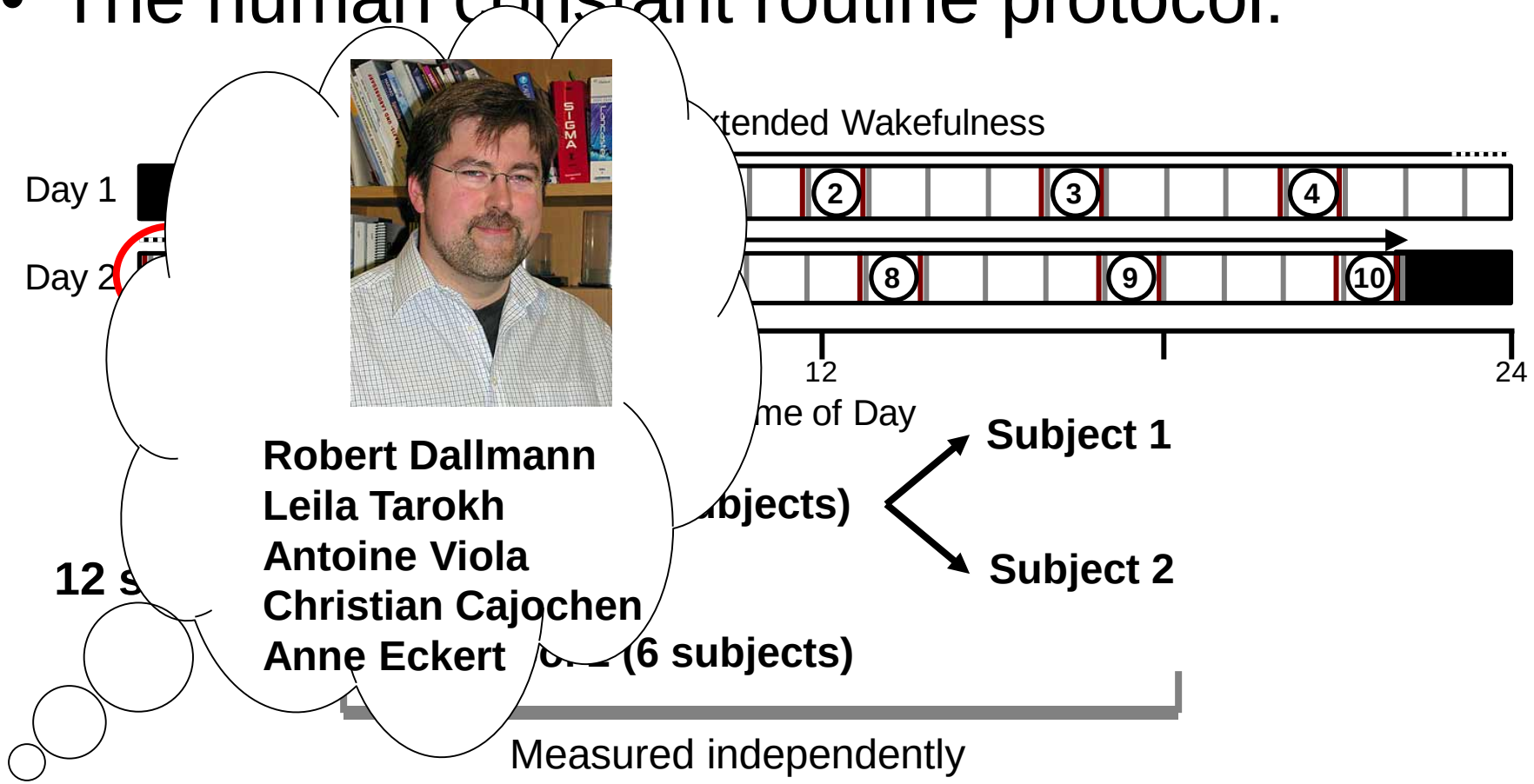
Of a total of 642 soluble liver proteins

Reddy, 2006

And not surprisingly, 20% of the mouse metabolome is also rhythmic…**(Minami 2009)**

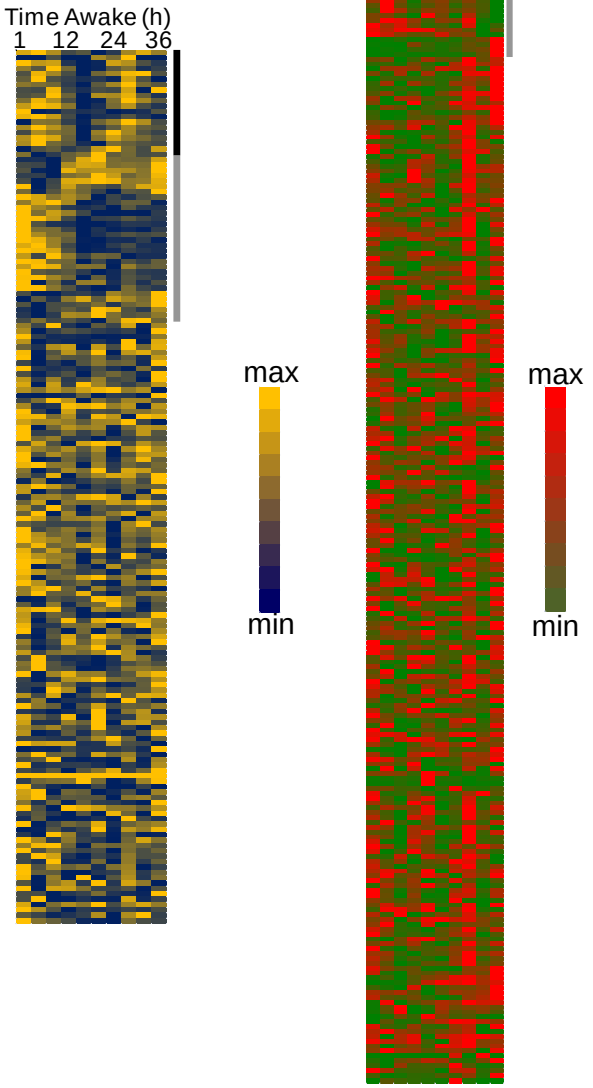
…but how much of this pattern is due to rhythmic food intake or sleep?

- The human constant routine protocol:

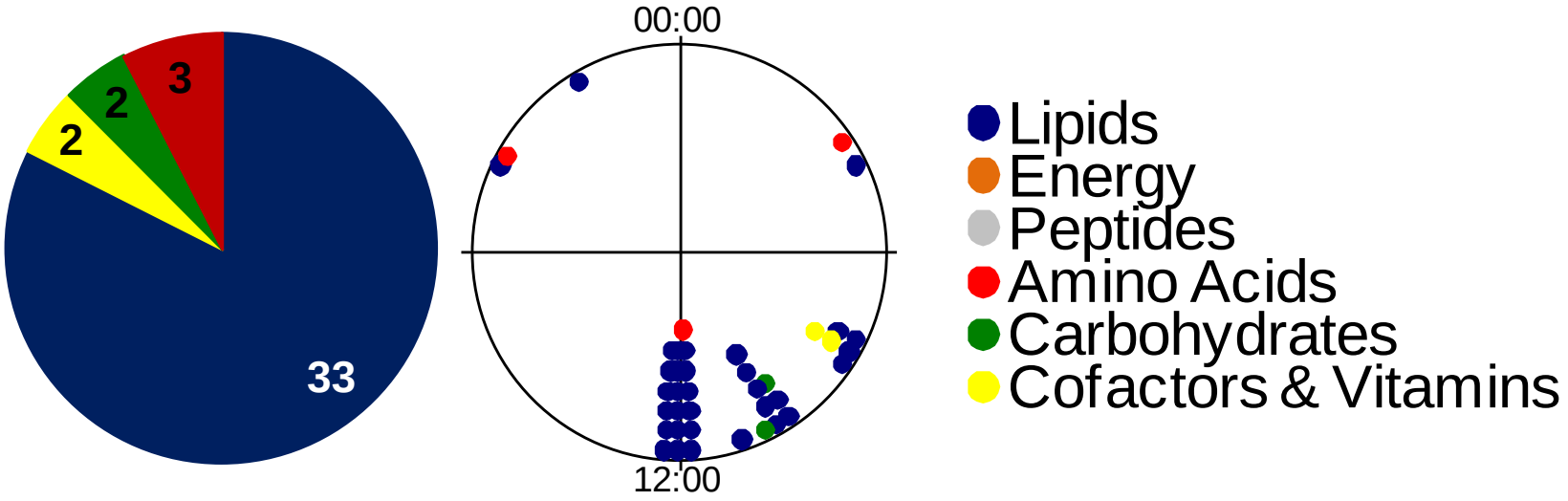


Overall results

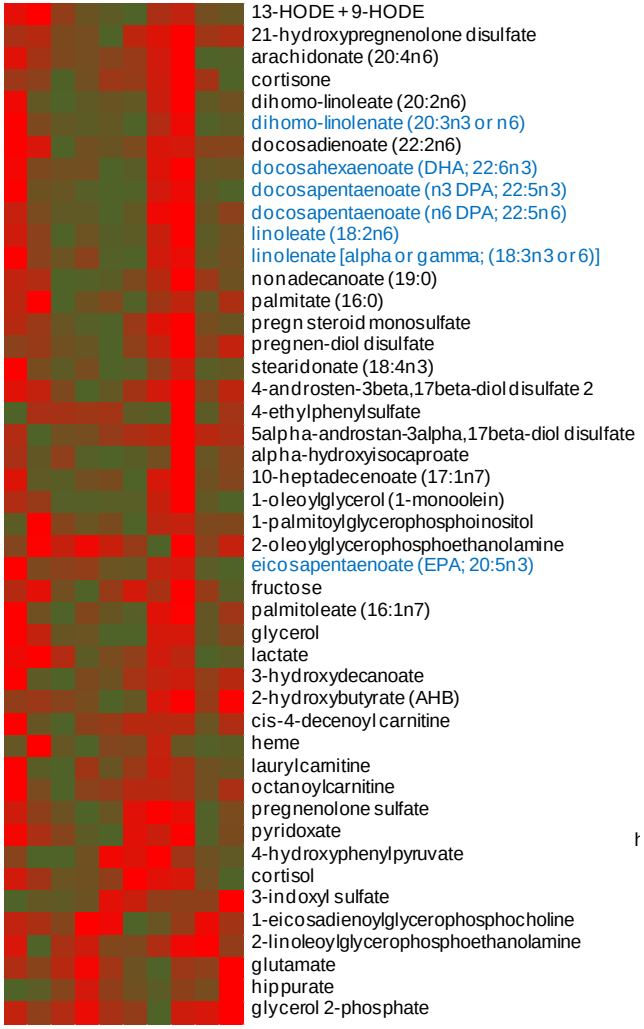
- Plasma
  - 281 metabolites
  - 41 circadian rhythmic
- Saliva
  - 178 metabolites
  - 29 circadian rhythmic

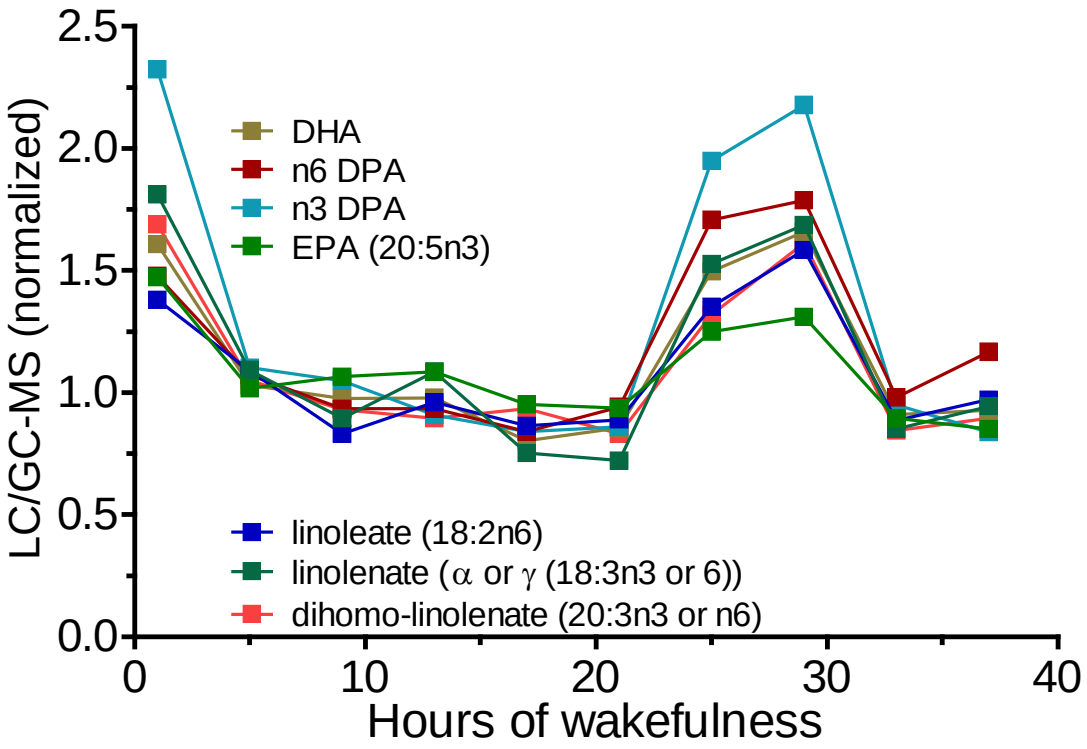


Rhythmic plasma metabolites

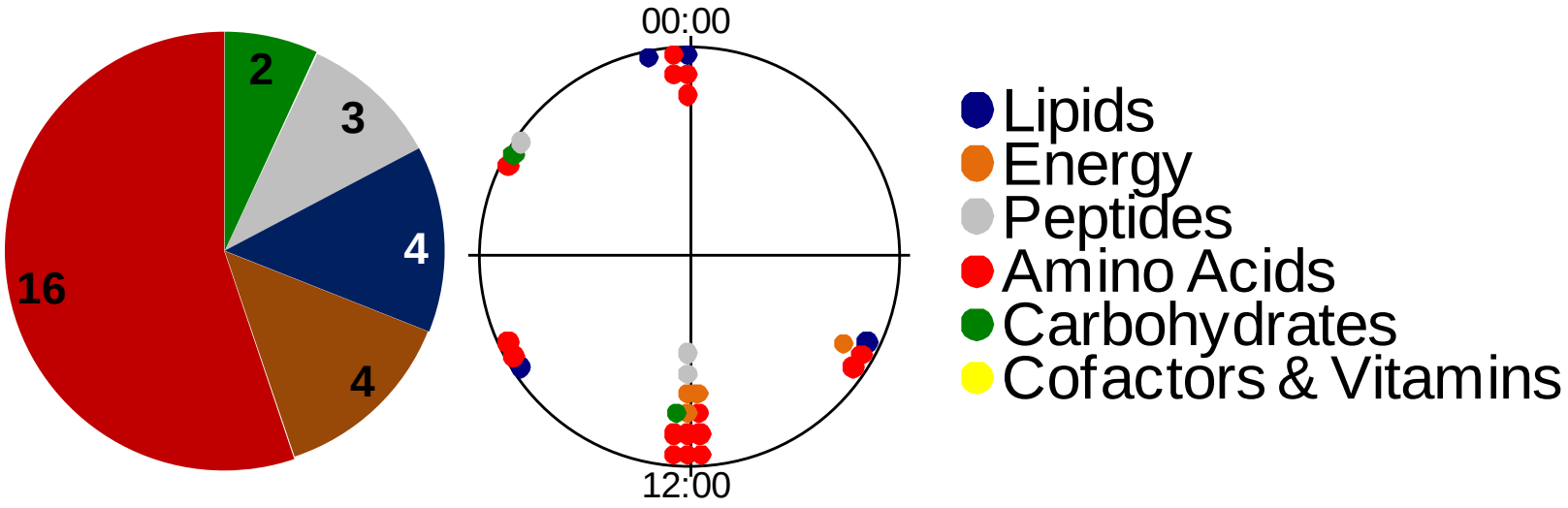


Rhythmic plasma metabolites

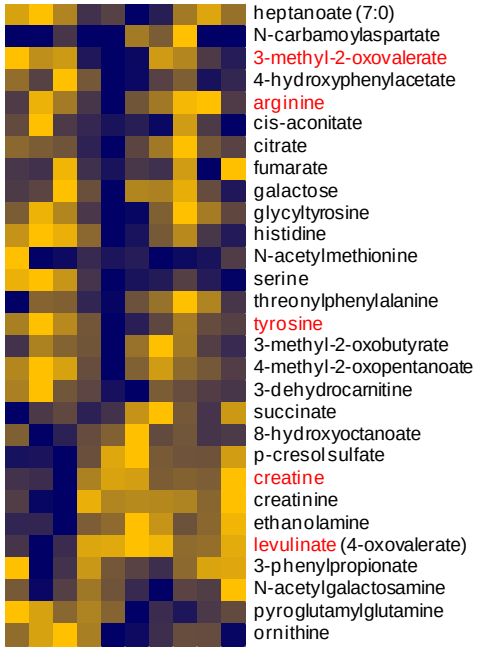


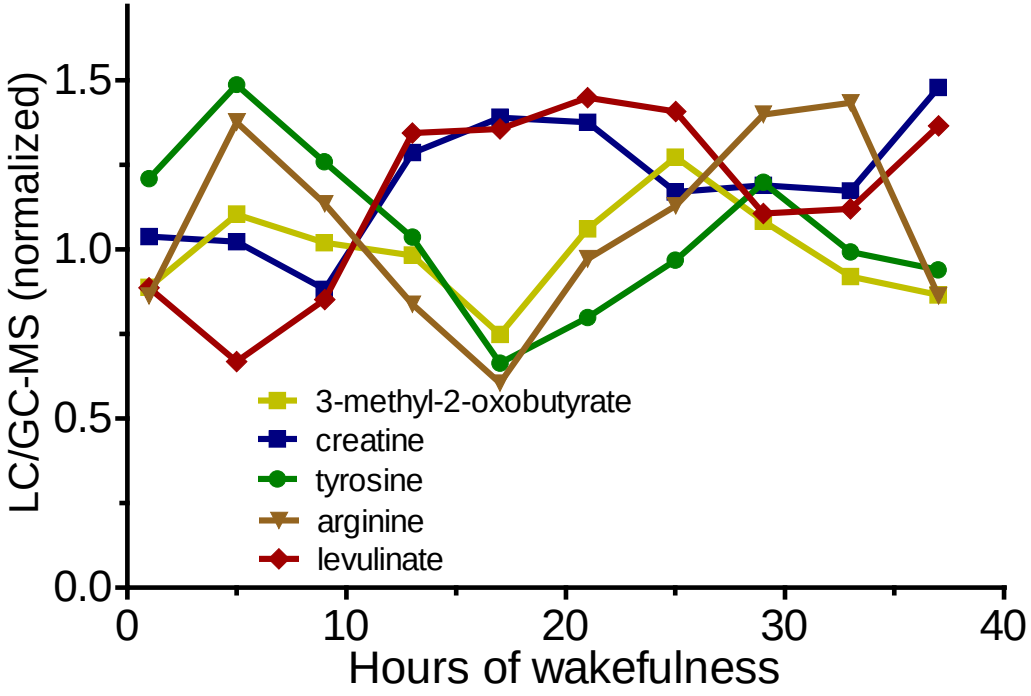


Rhythmic saliva metabolites



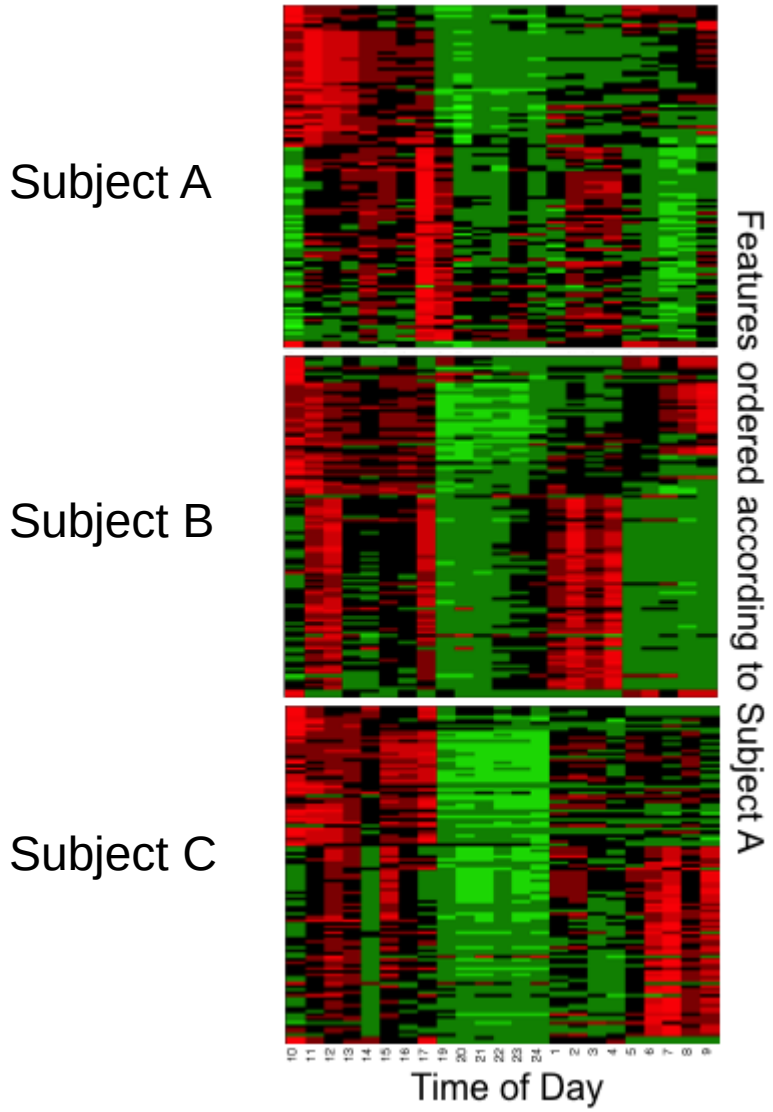
Rhythmic saliva metabolites





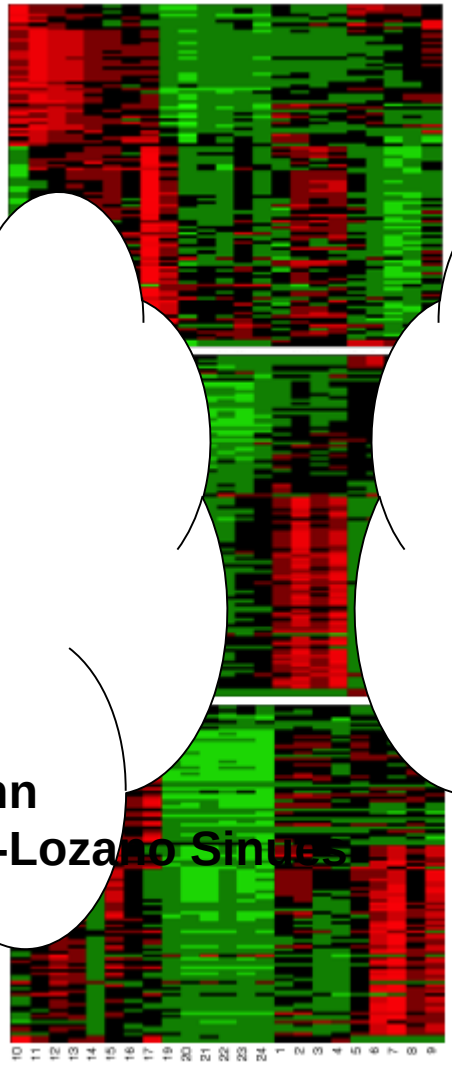
The next step: Metabolic breathylomics directly in the clinic

Human circadian breath metabolome from 3 subjects



Human circadian breath metabolome from 3 subjects

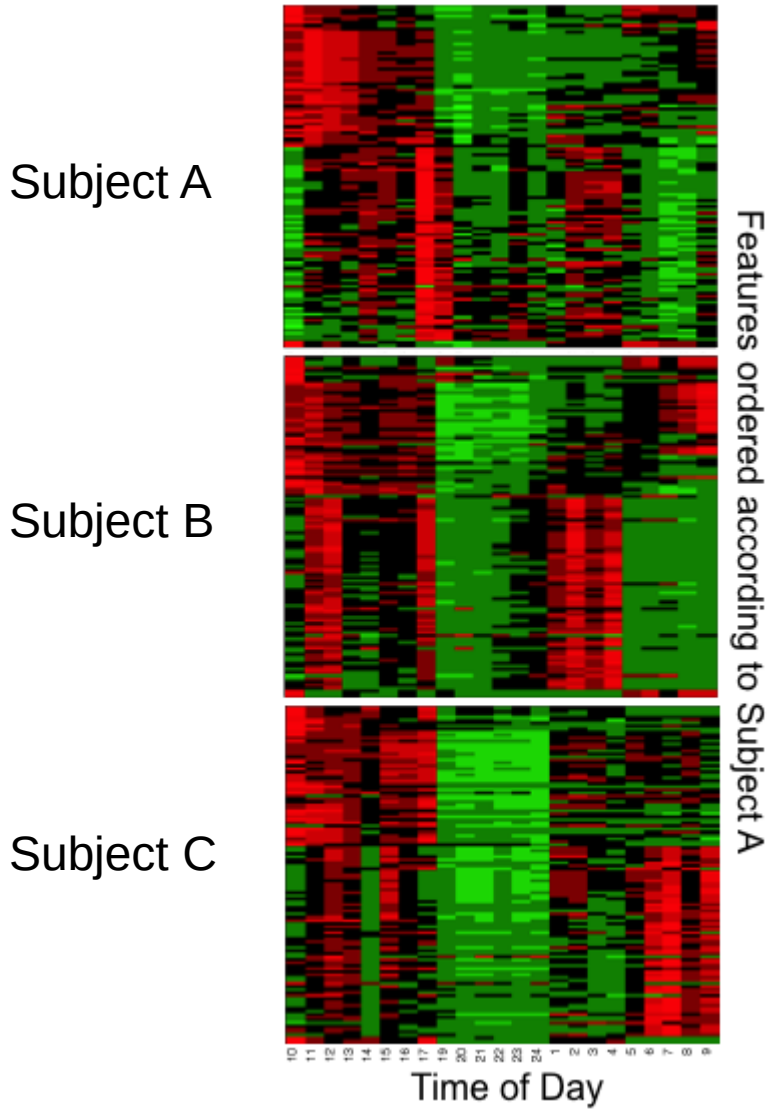
Subject A



Robert Dallmann
Pablo Martinez-Lozano Sinues

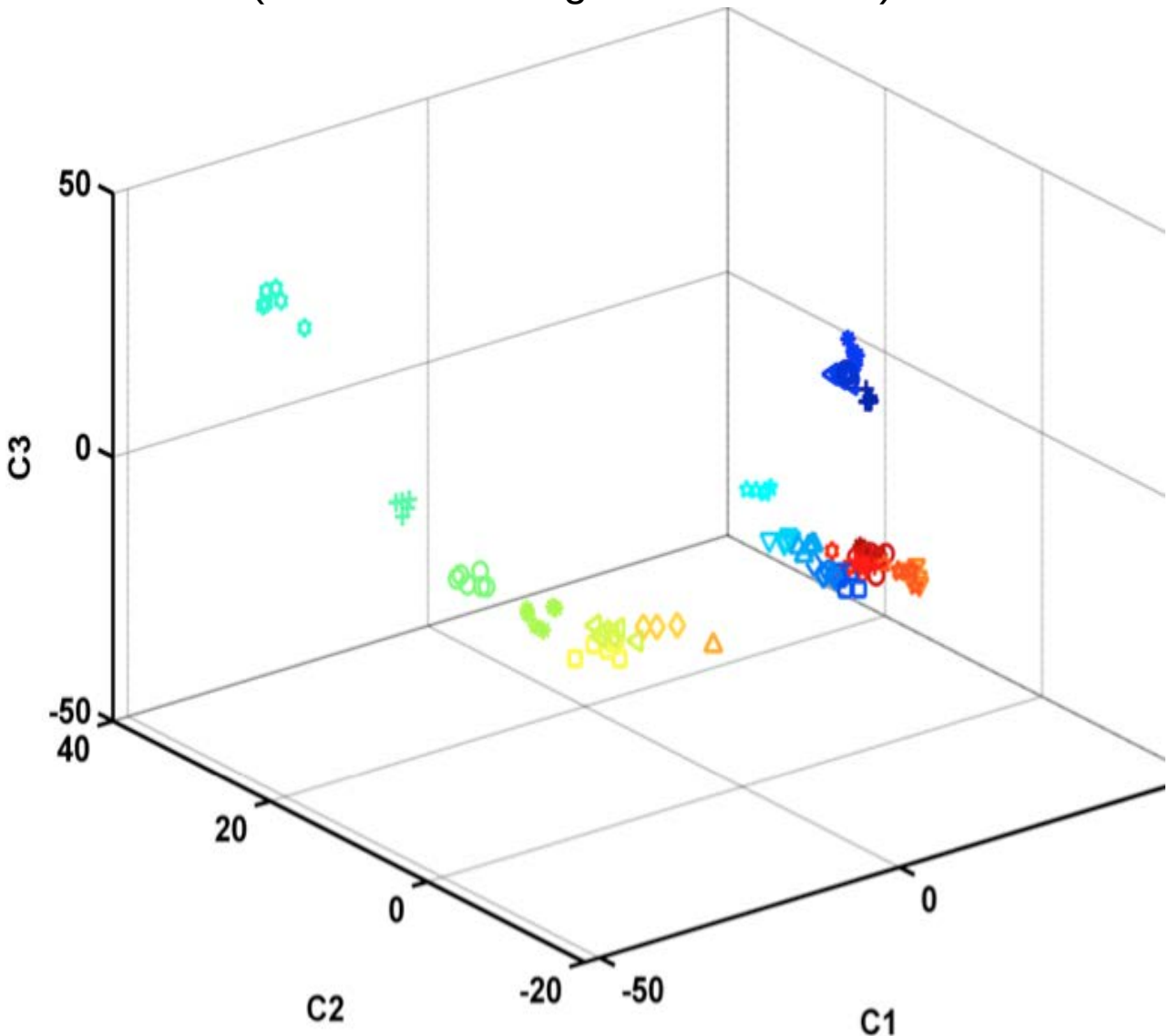
Leila Tarokh
Renato Zenobi

Human circadian breath metabolome from 3 subjects

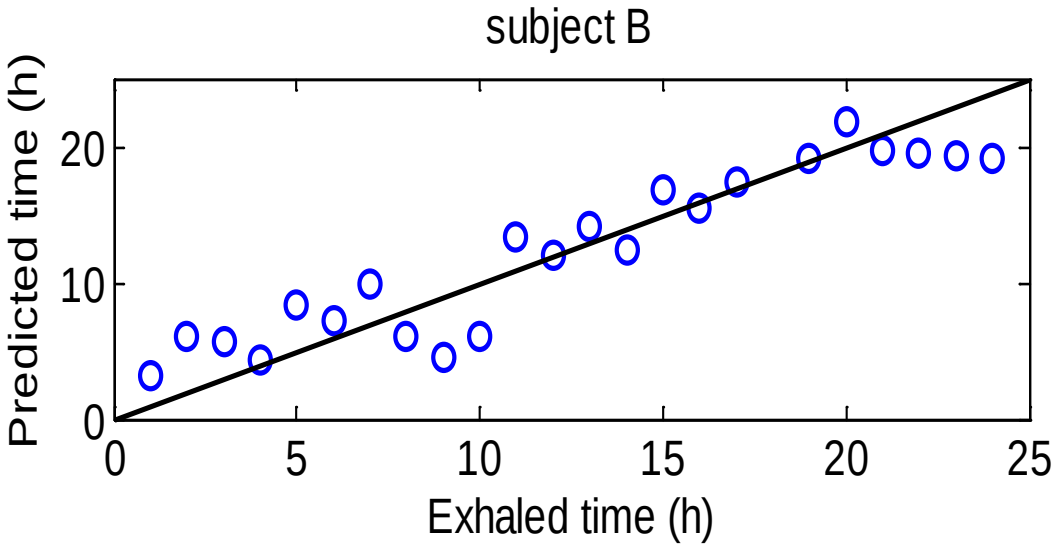


Supervised PCA of Breath Metabolome of One Subject during 24 hours

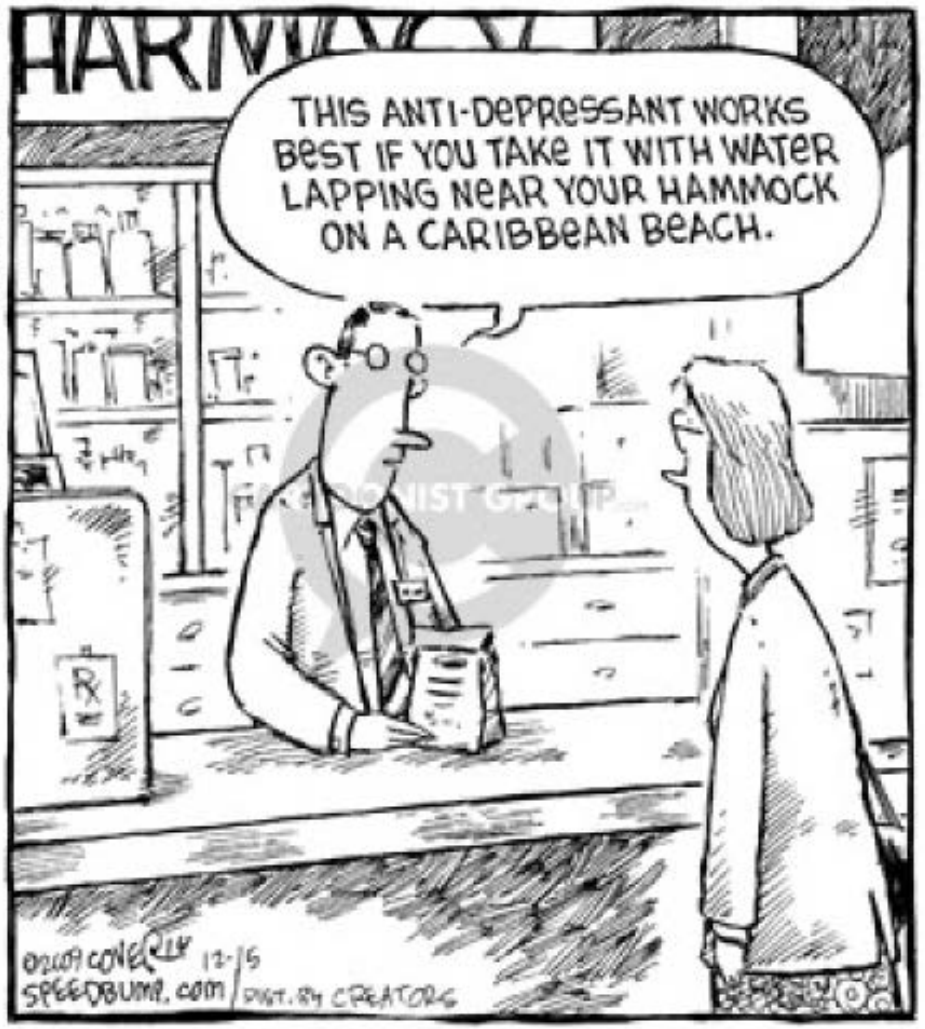
(similar colors sign. similar times)



Breathprint predicts time of day ±3hrs



Why is circadian time relevant to medicine?



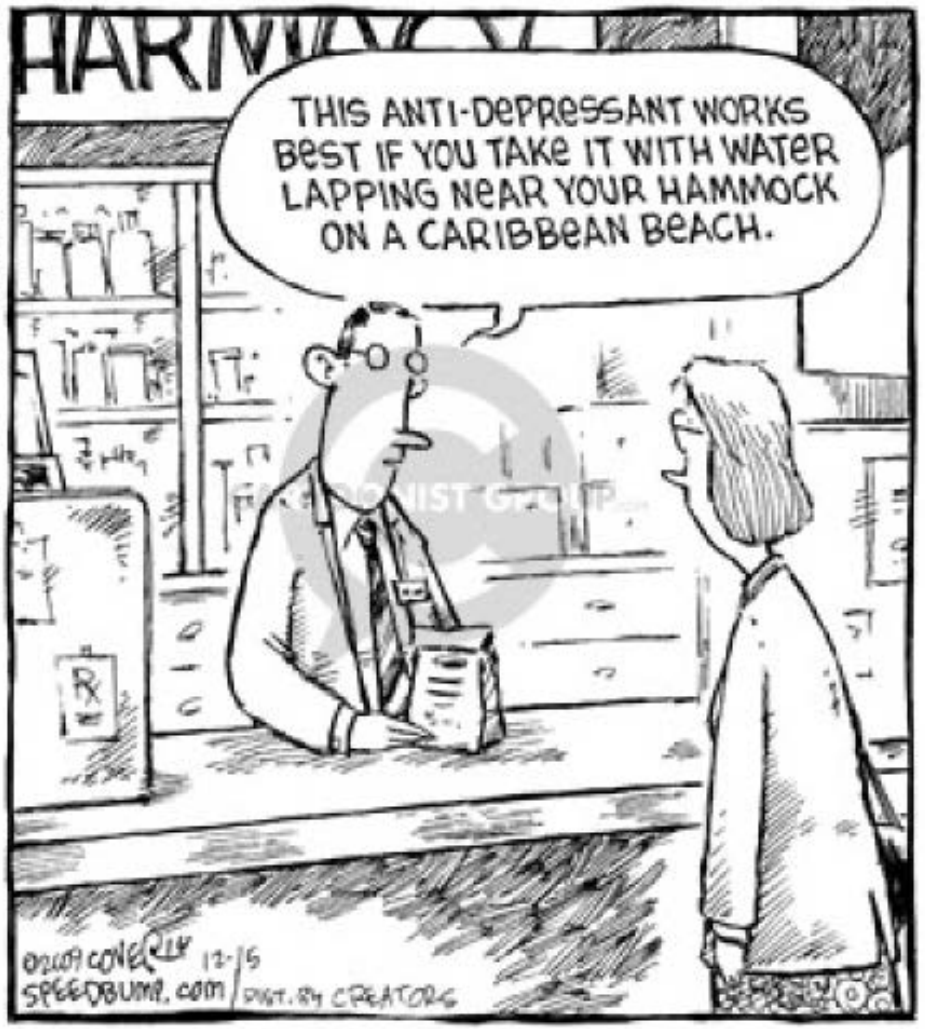
Most drugs work better under certain conditions.

- Better in some people than in others.

-Better in conjunction with another drug.

-Better at a particular time of day.

Why is circadian time relevant to medicine?



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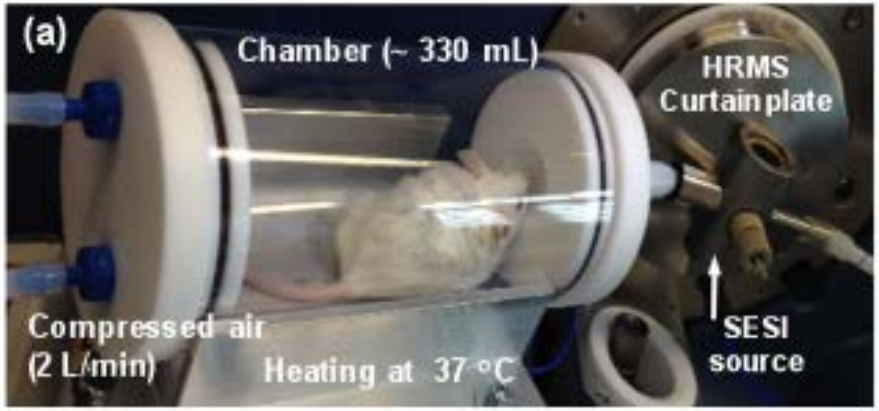
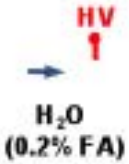
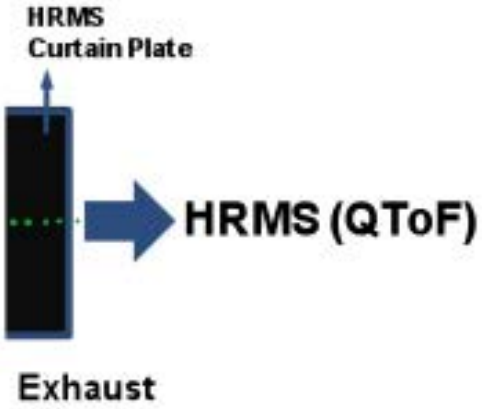
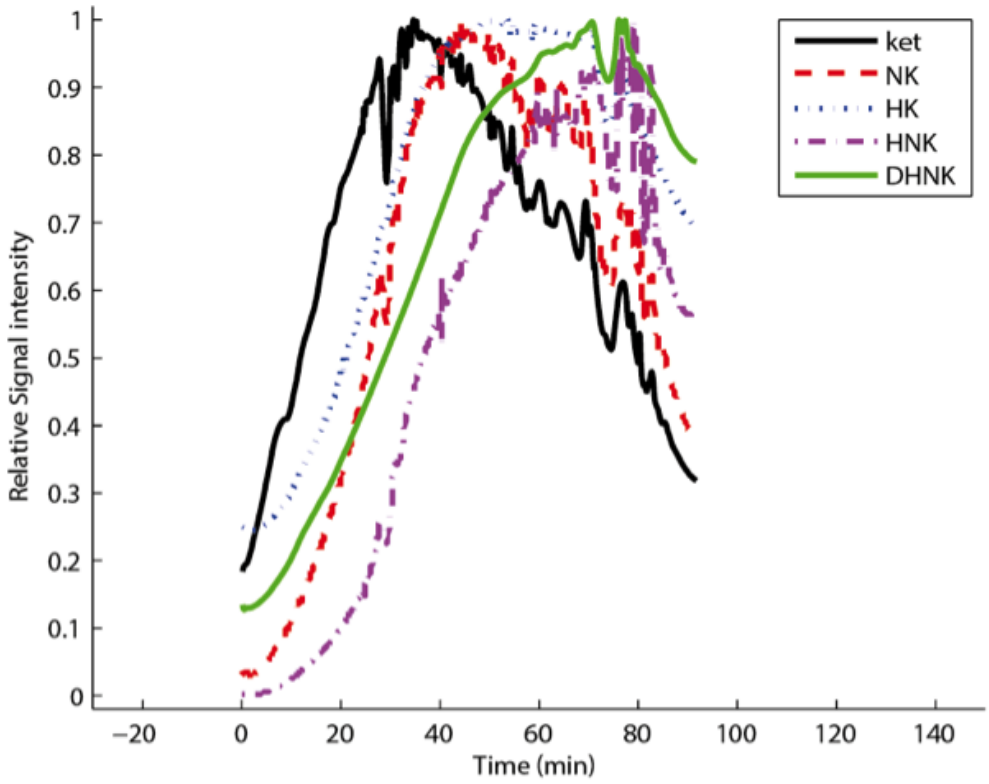
Set-up for mouse breath analysis





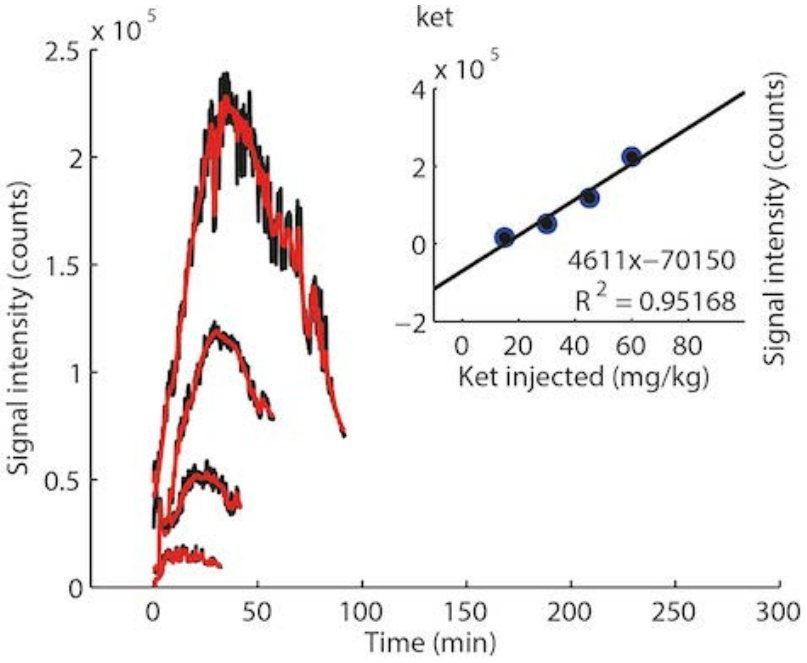


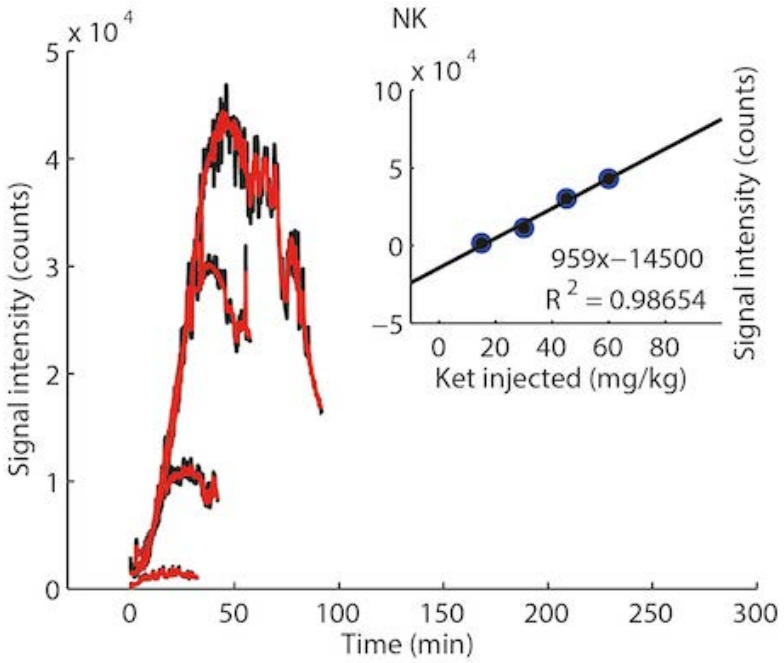
PK curve for ket and metabolites



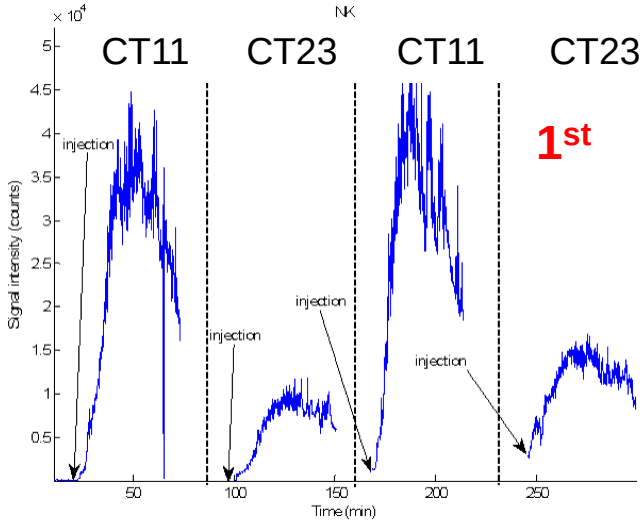
Normalized signal intensity for ketamine and its metabolites detected in the breath of a mouse injected with 60 mg/kg of ketamine. Note the different kinetics. Peaking times are: Ketamine Ket= 34.5; Norketamine NK= 46; Hydroketamine HK= 51; Hydronorketamine HNK and Dihydronorketamine DHNK= 77 min.

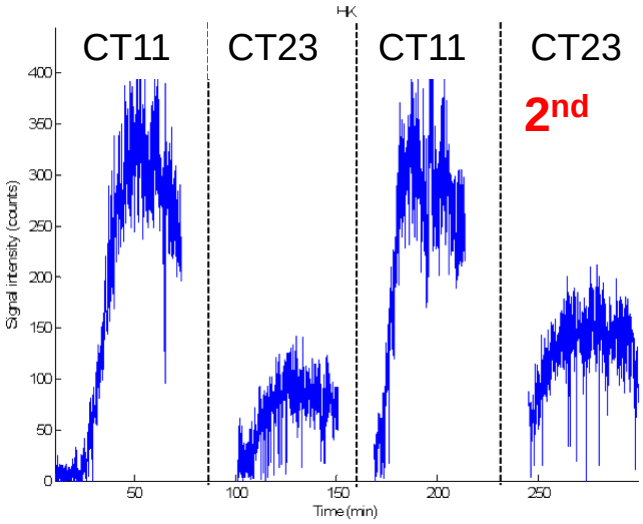
Dose response for ket and nk

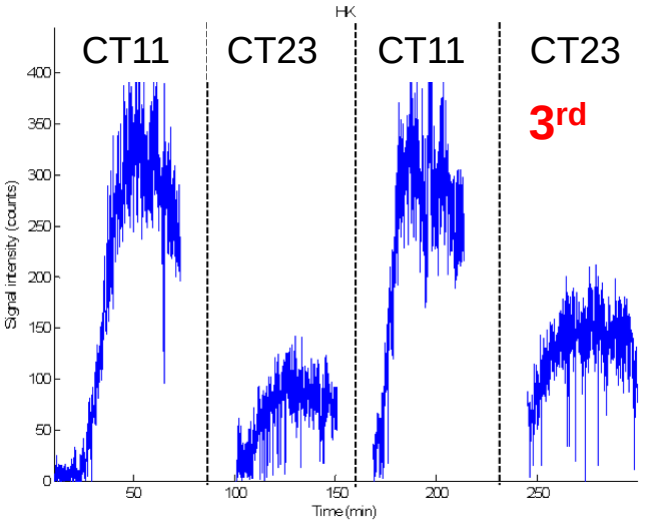




Circadian modulation of ket metabolites

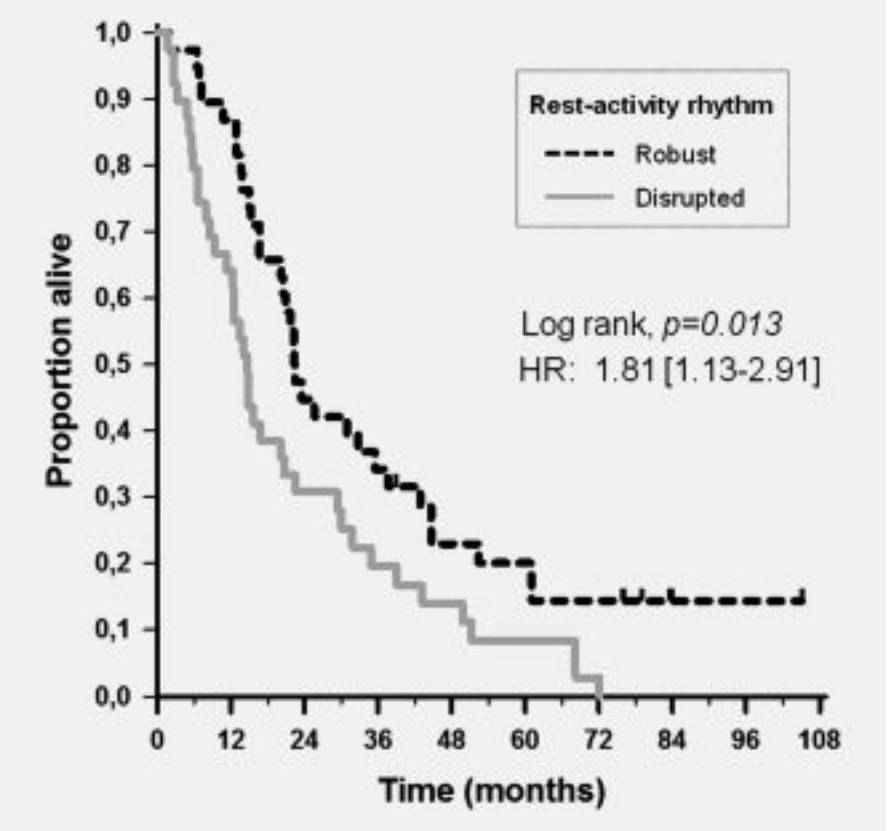






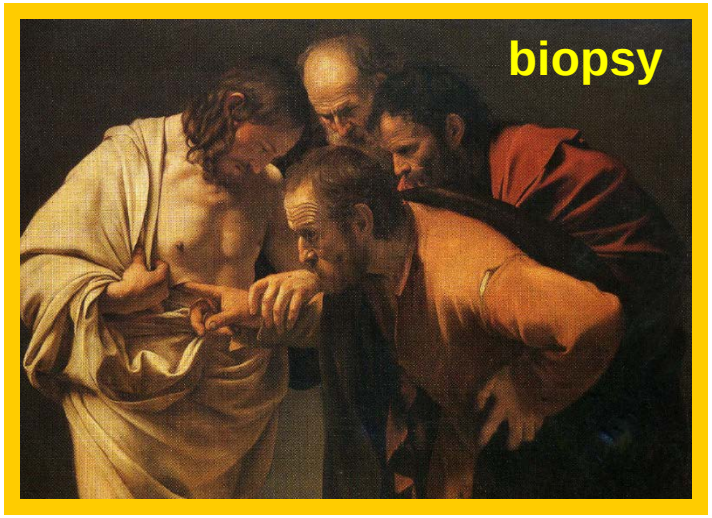
A current challenge in medicine: identifying when timing matters.

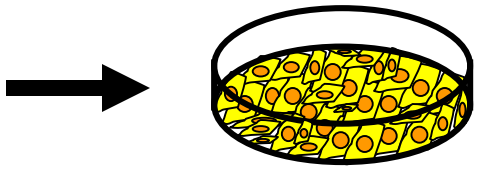
Circadian behavior predicts chemotherapy survival in humans.

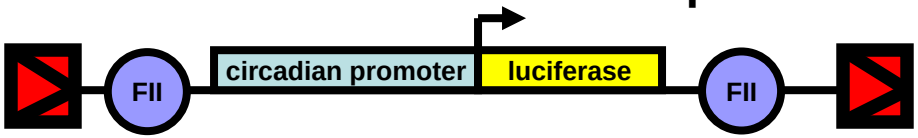


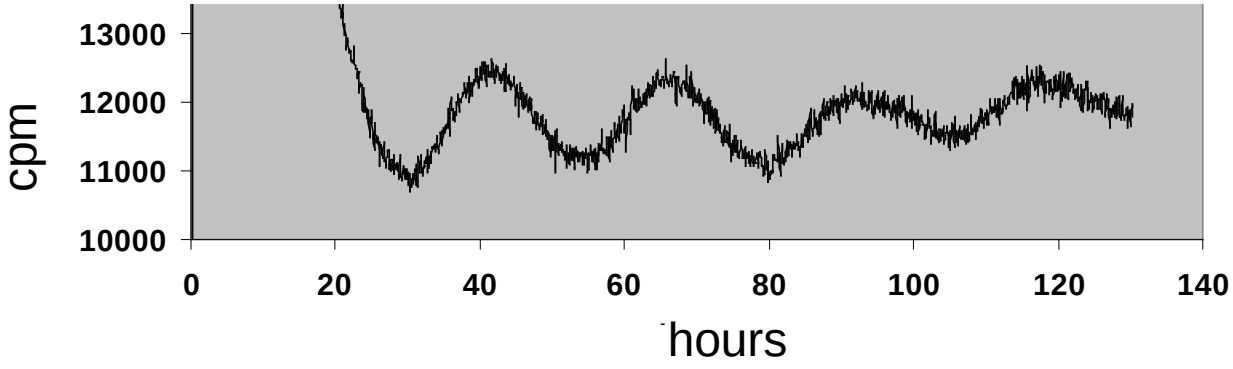
(Innominato et al., 2012)

Methods: measuring cellular clocks

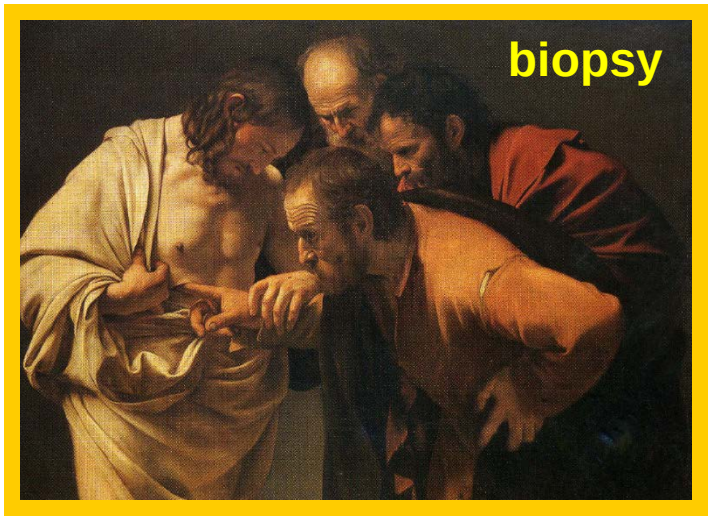


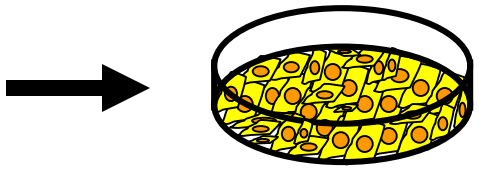


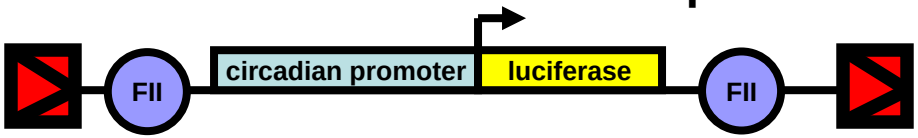




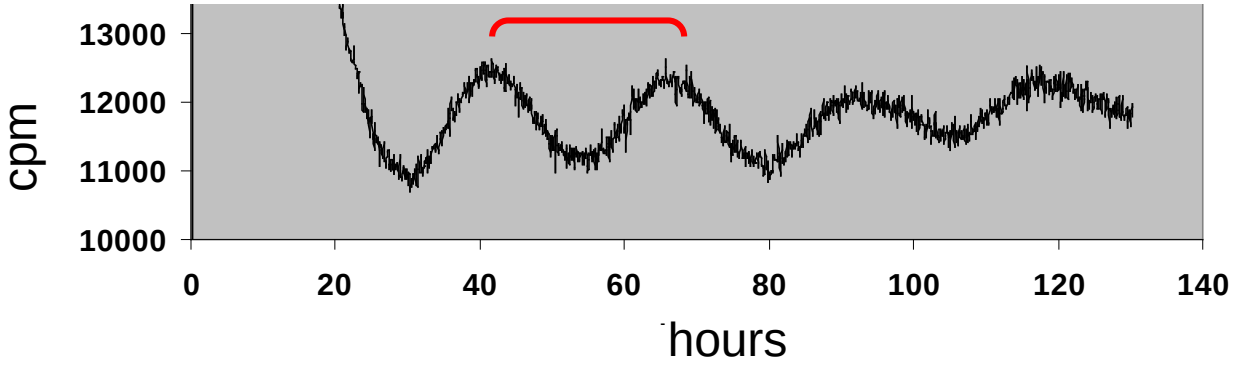
Methods: measuring cellular clocks



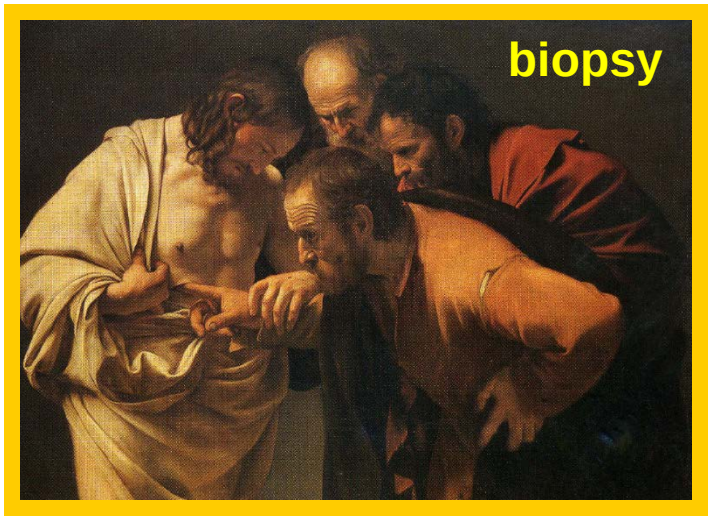


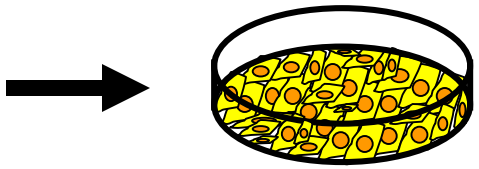


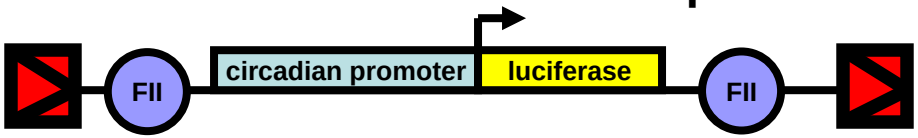
Period length: the time for 1 cycle



Methods: measuring cellular clocks







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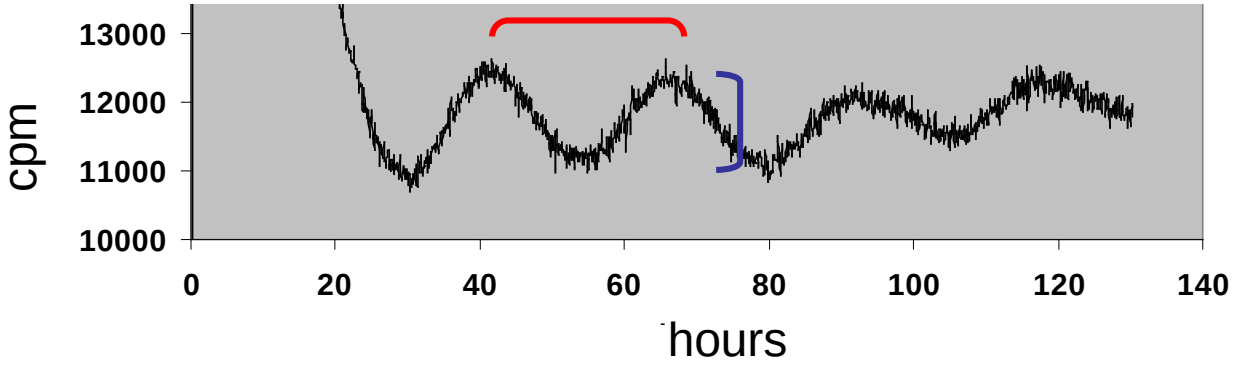
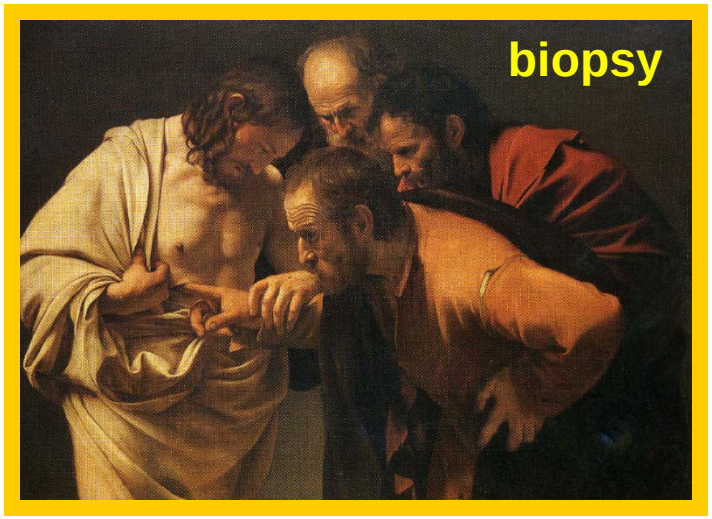
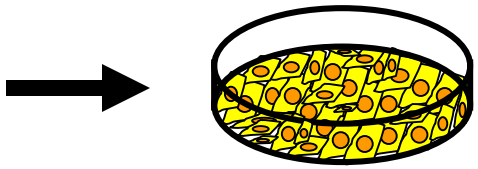
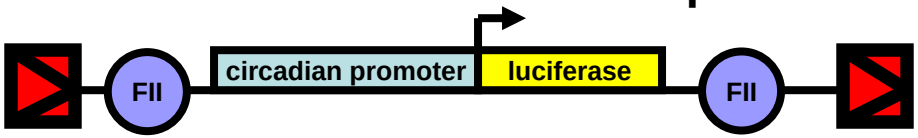


Amplitude:
The ratio of max to min expression

Methods: measuring cellular clocks







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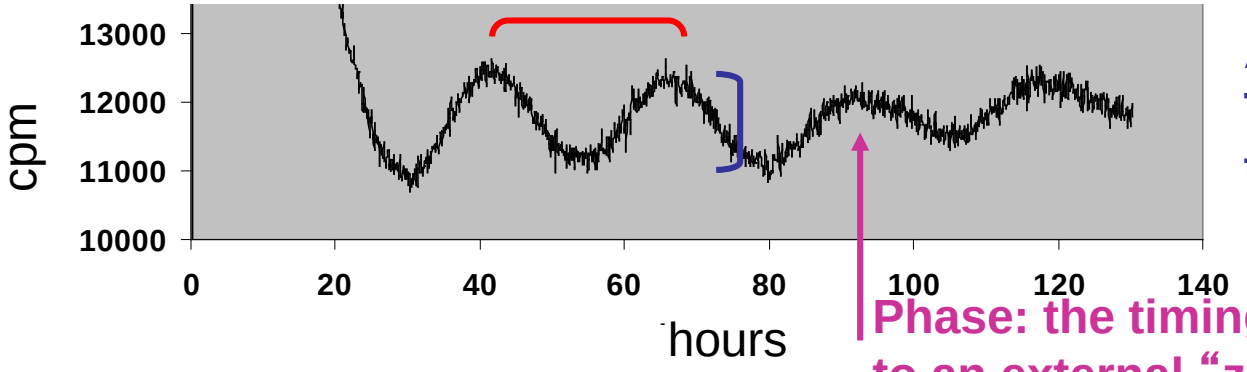
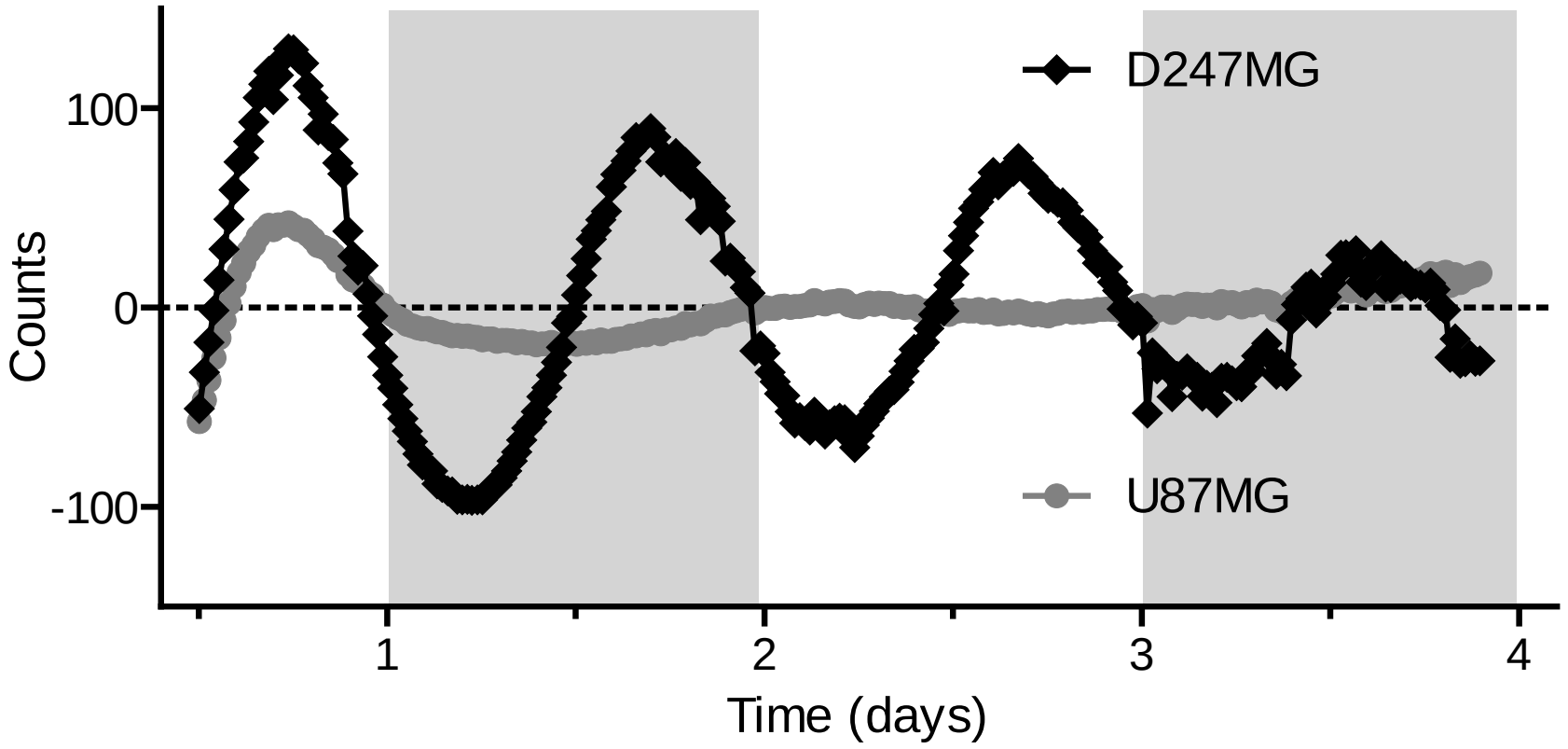


Amplitude:
The ratio of max to min expression

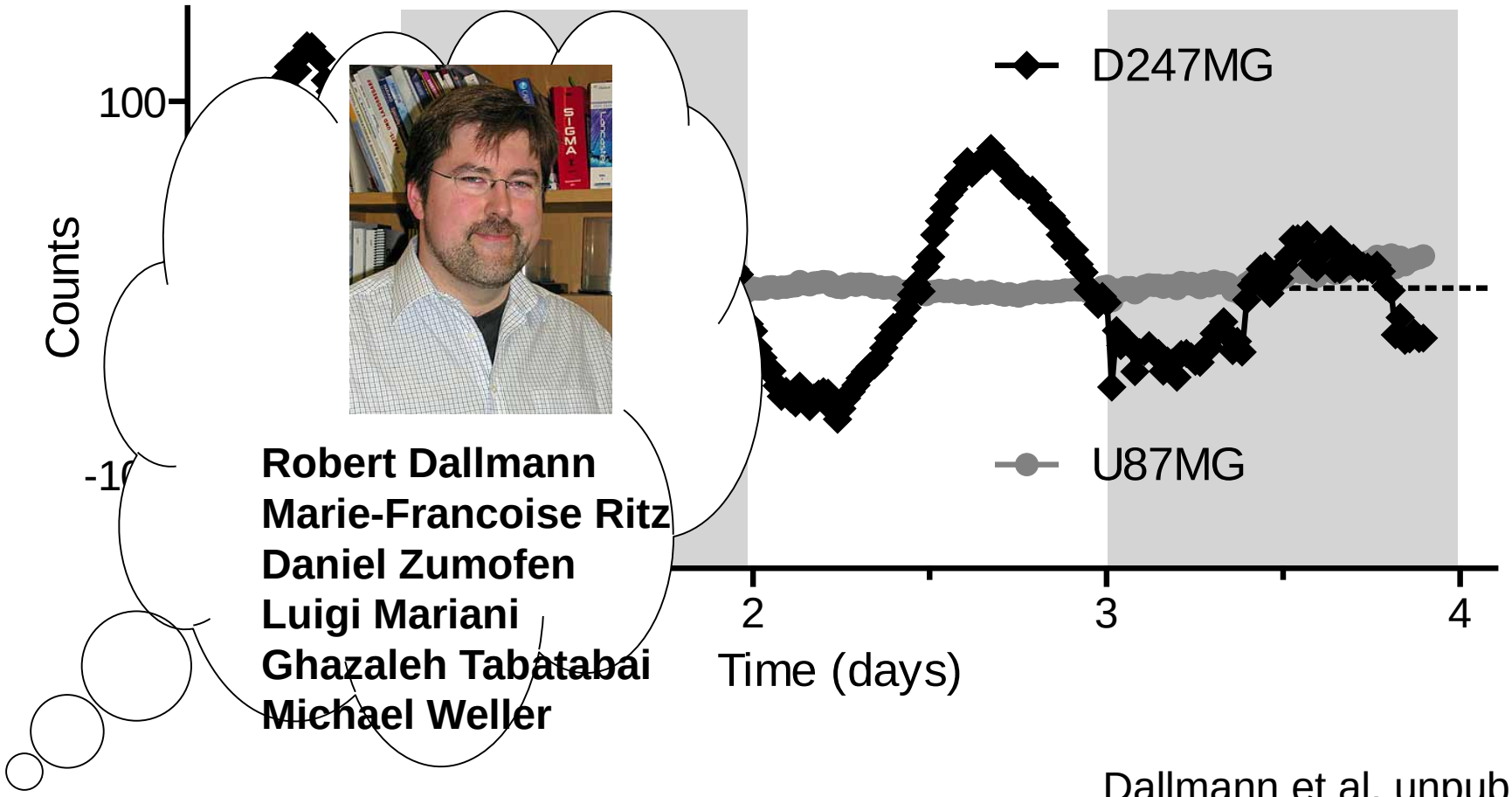
Phase: the timing of each cycle relative to an external "zeitgeber"

Clock in glioblastoma cell lines



Dallmann et al. unpublished

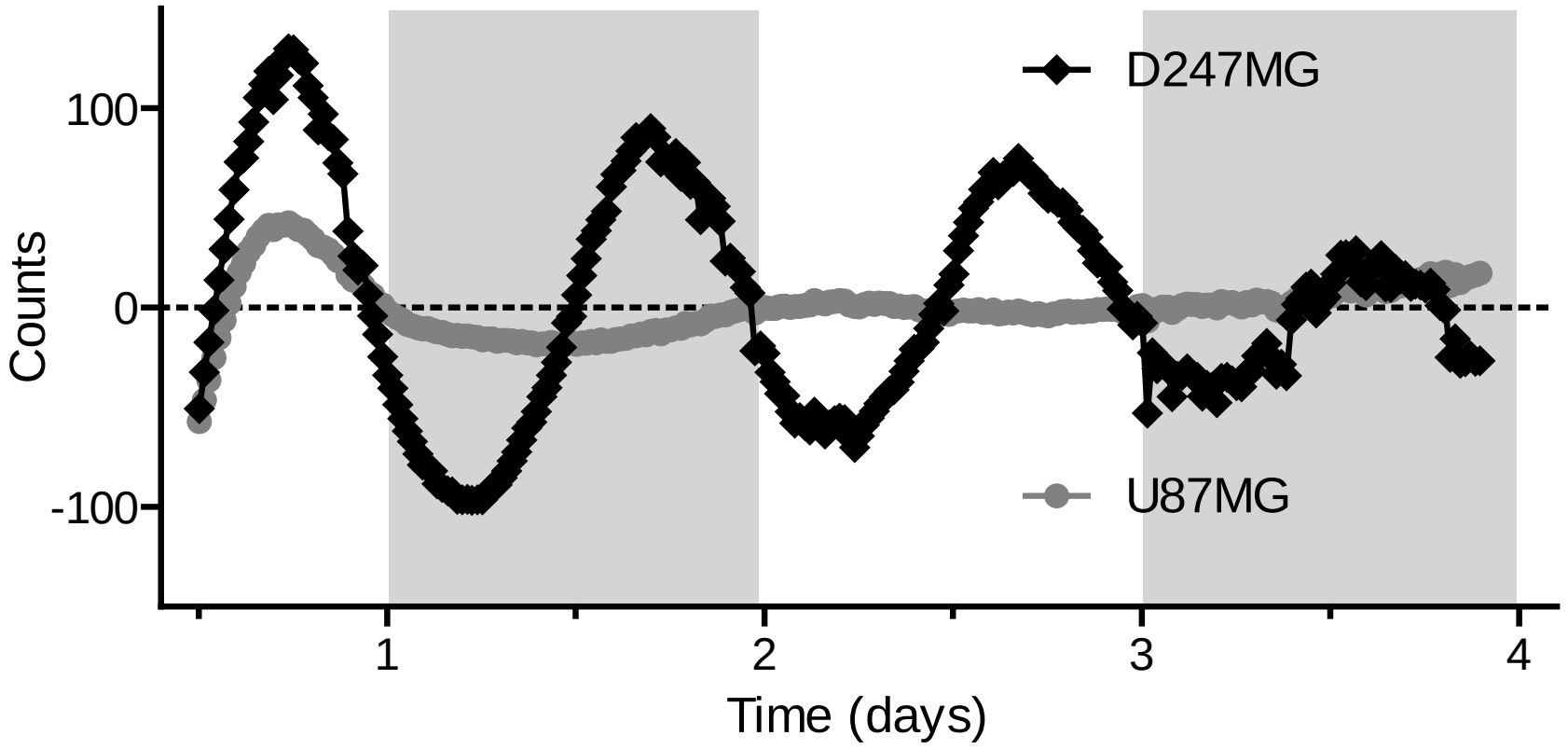
Clock in glioblastoma cell lines



Robert Dallmann
Marie-Francoise Ritz
Daniel Zumofen
Luigi Mariani
Ghazaleh Tabatabai
Michael Weller

Dallmann et al. unpublished

Clock in glioblastoma cell lines



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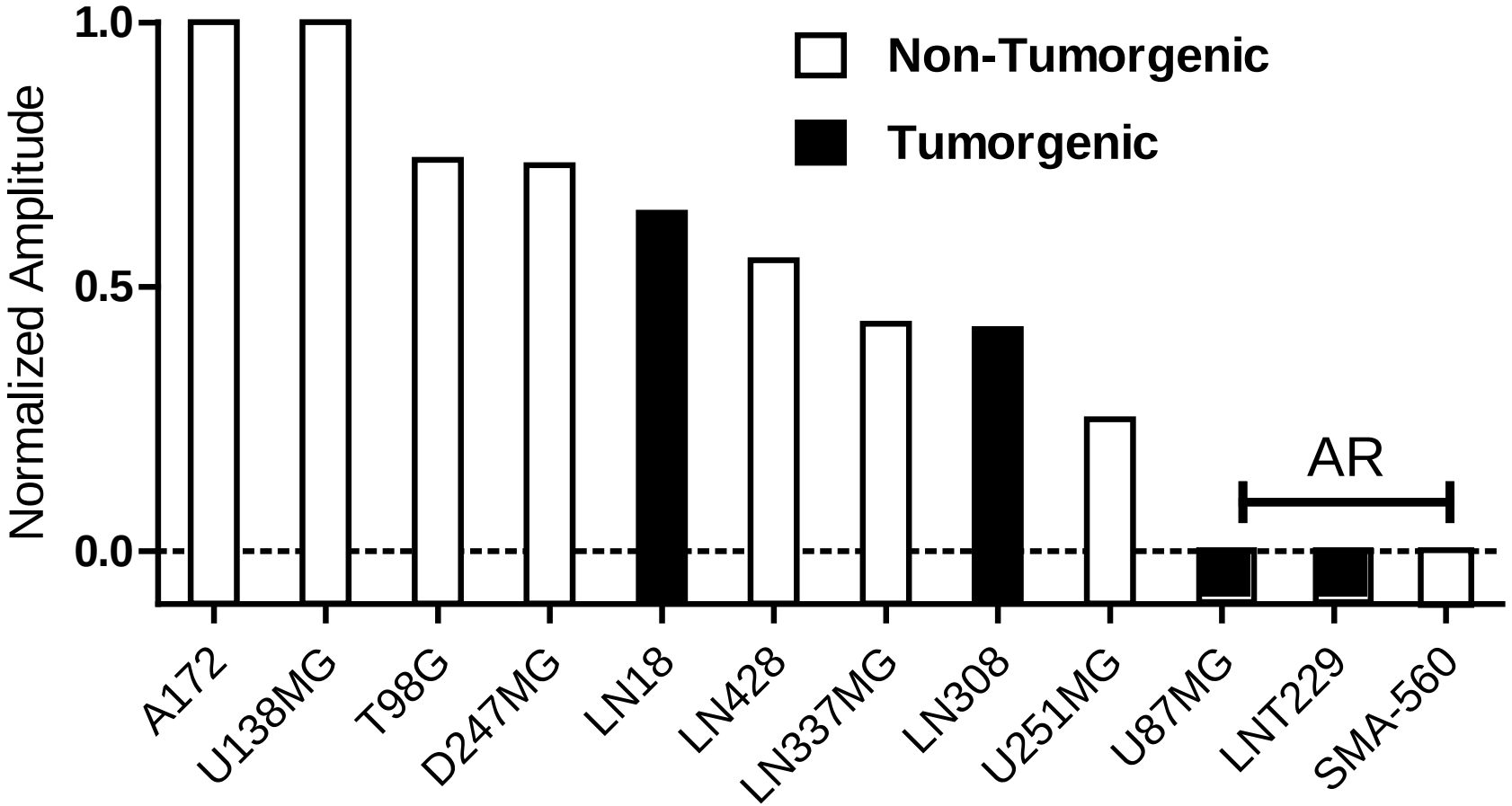
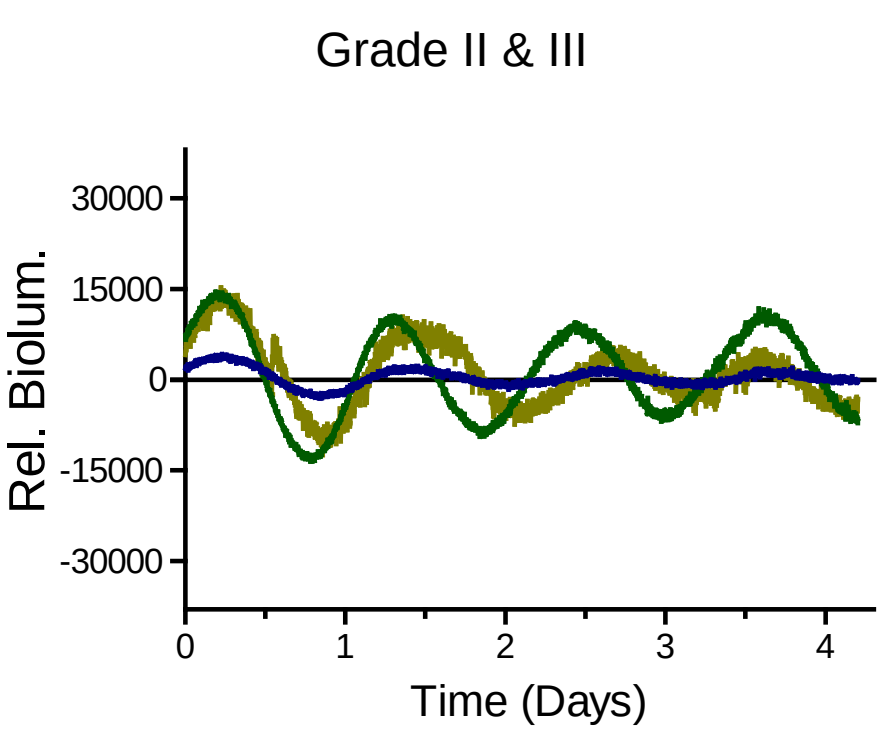
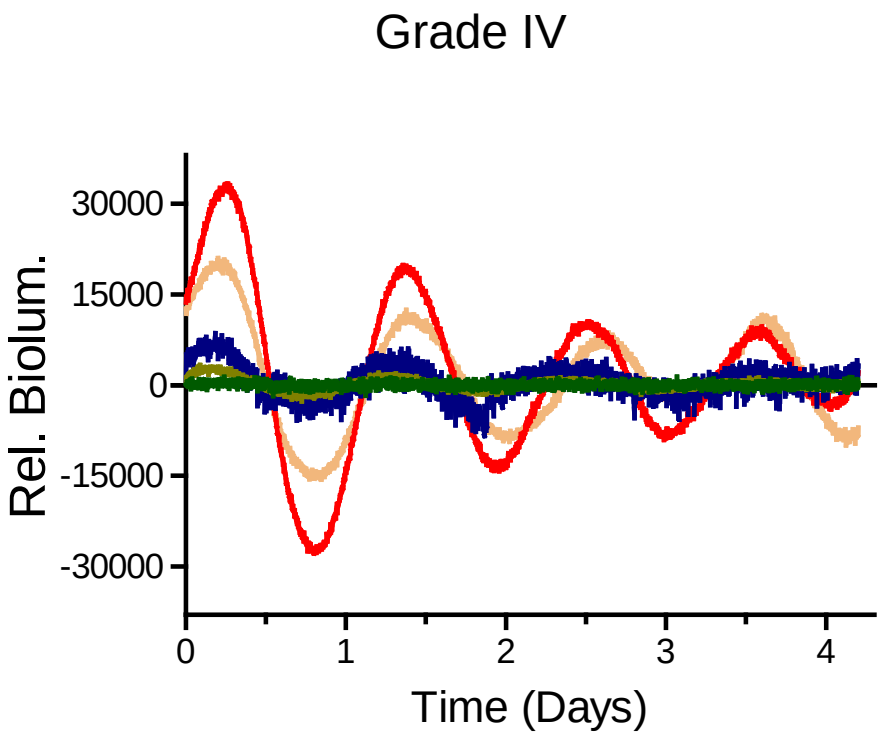


Dallmann et al. unpublished

Clocks in GBM

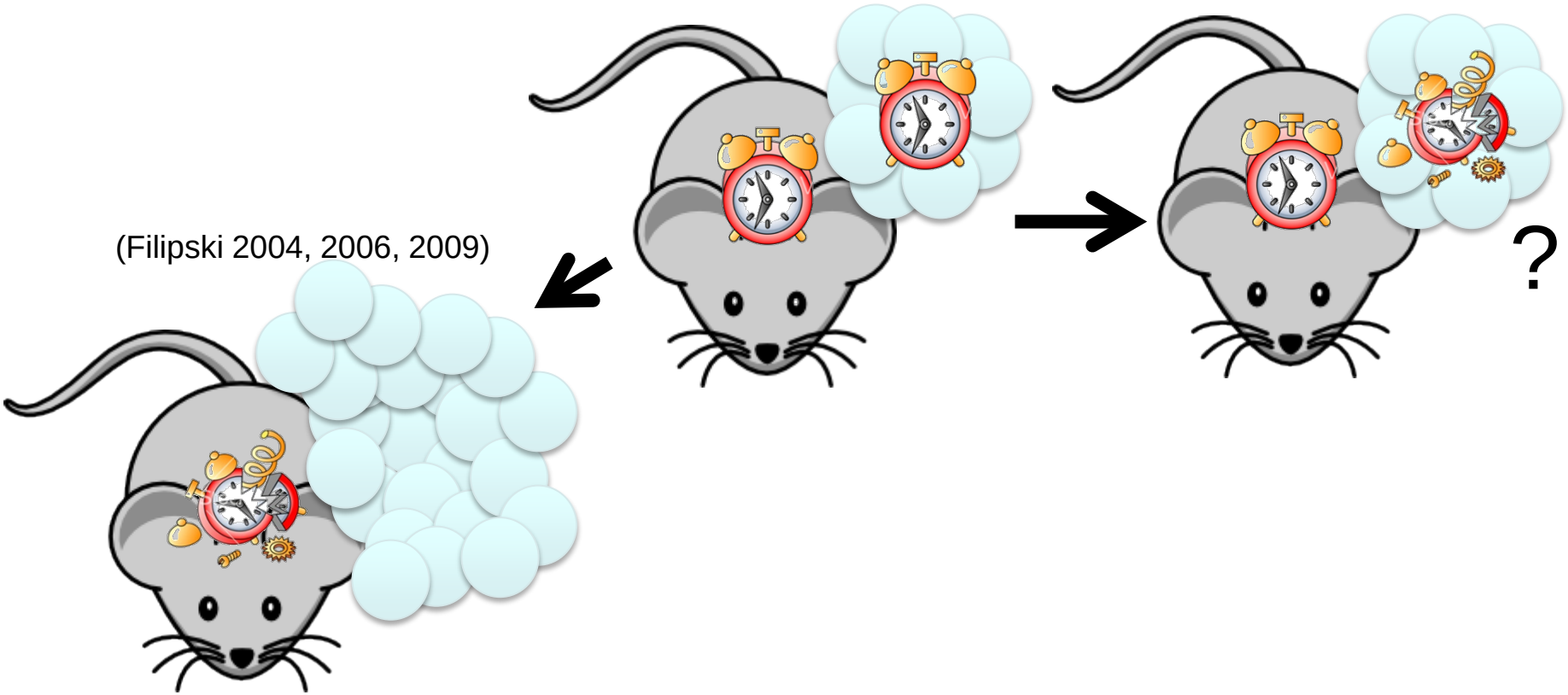




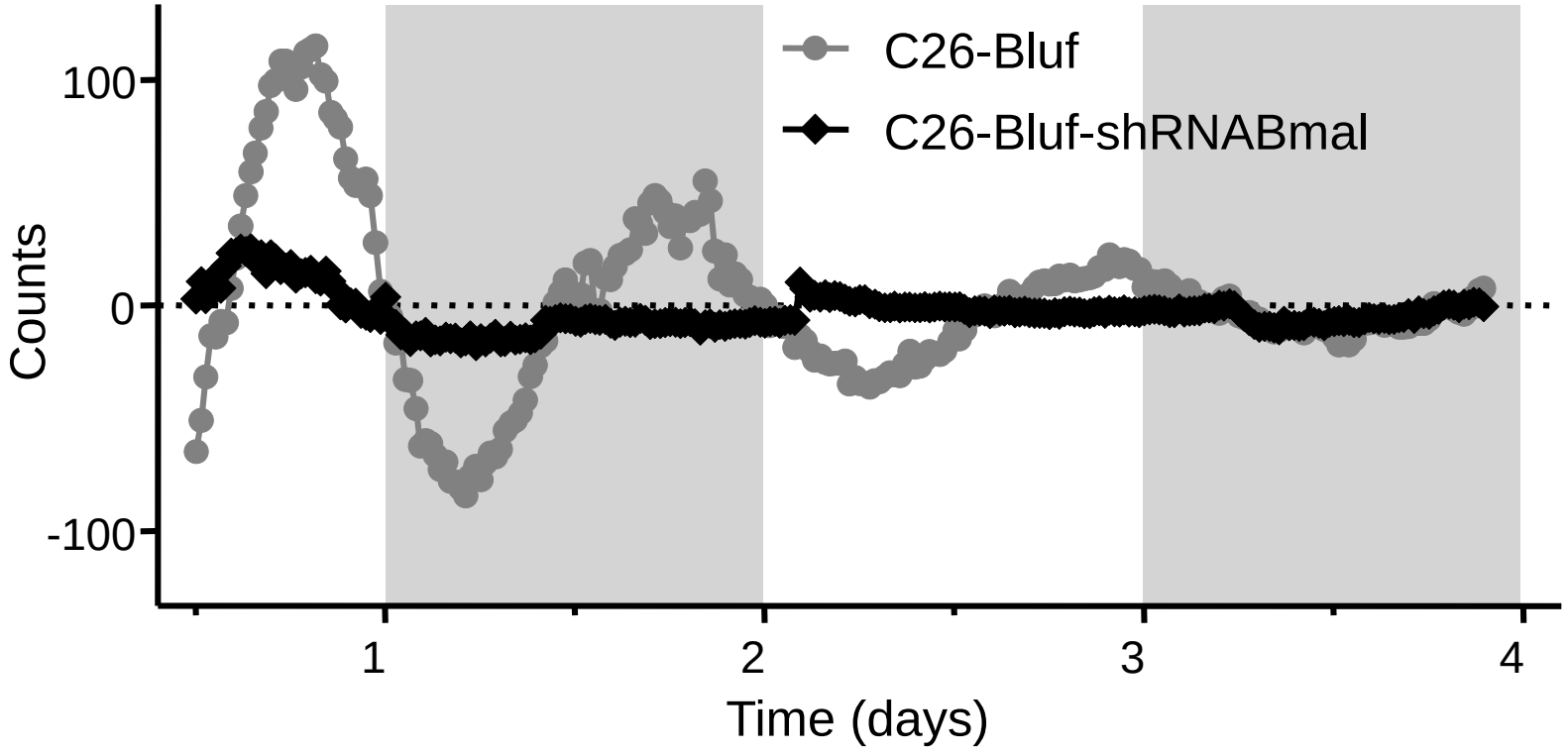
Dallmann, Ritz et al. unpublished

Are these differences relevant for cancer progression?

(Filipski 2004, 2006, 2009)

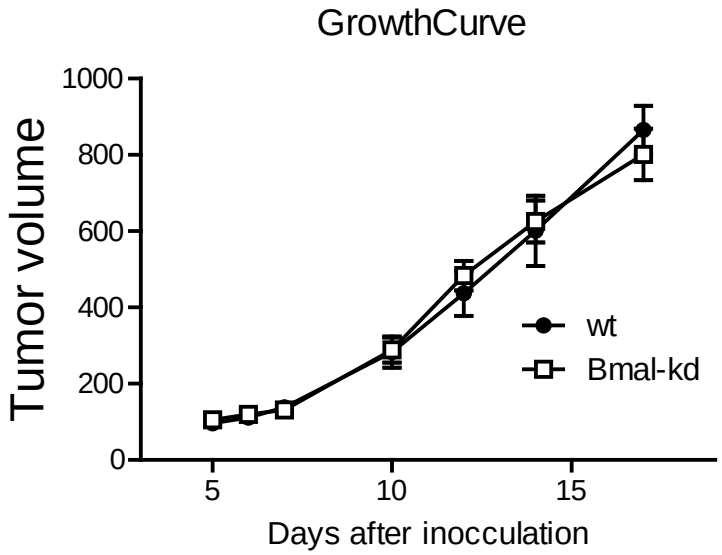


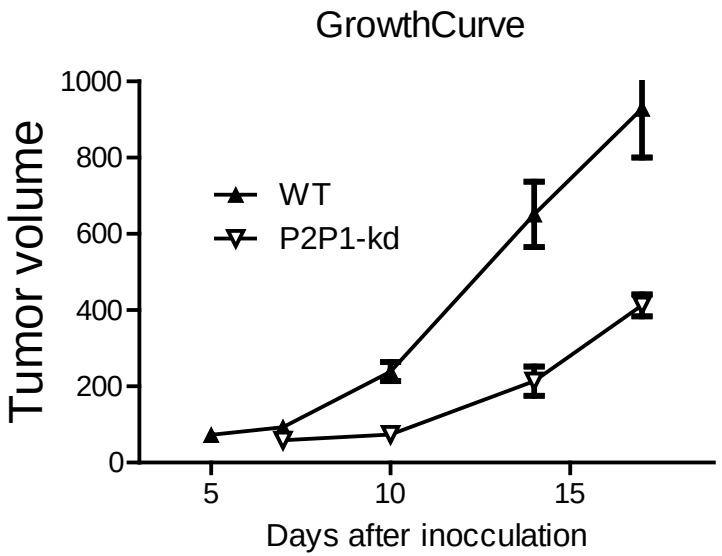
Killing the clock in a cancer cell line



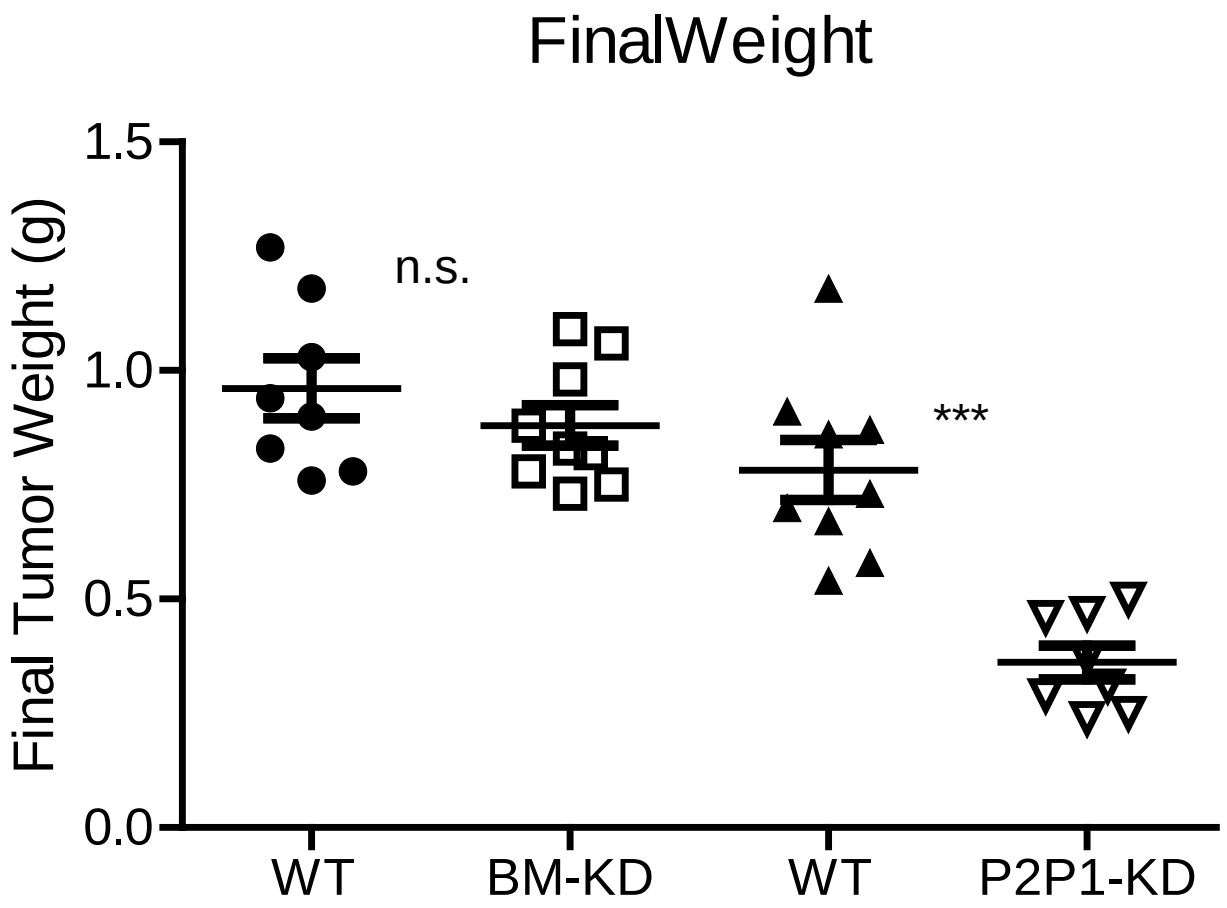
Dallmann et al. unpublished

Breaking the clock in C26 in 2 ways

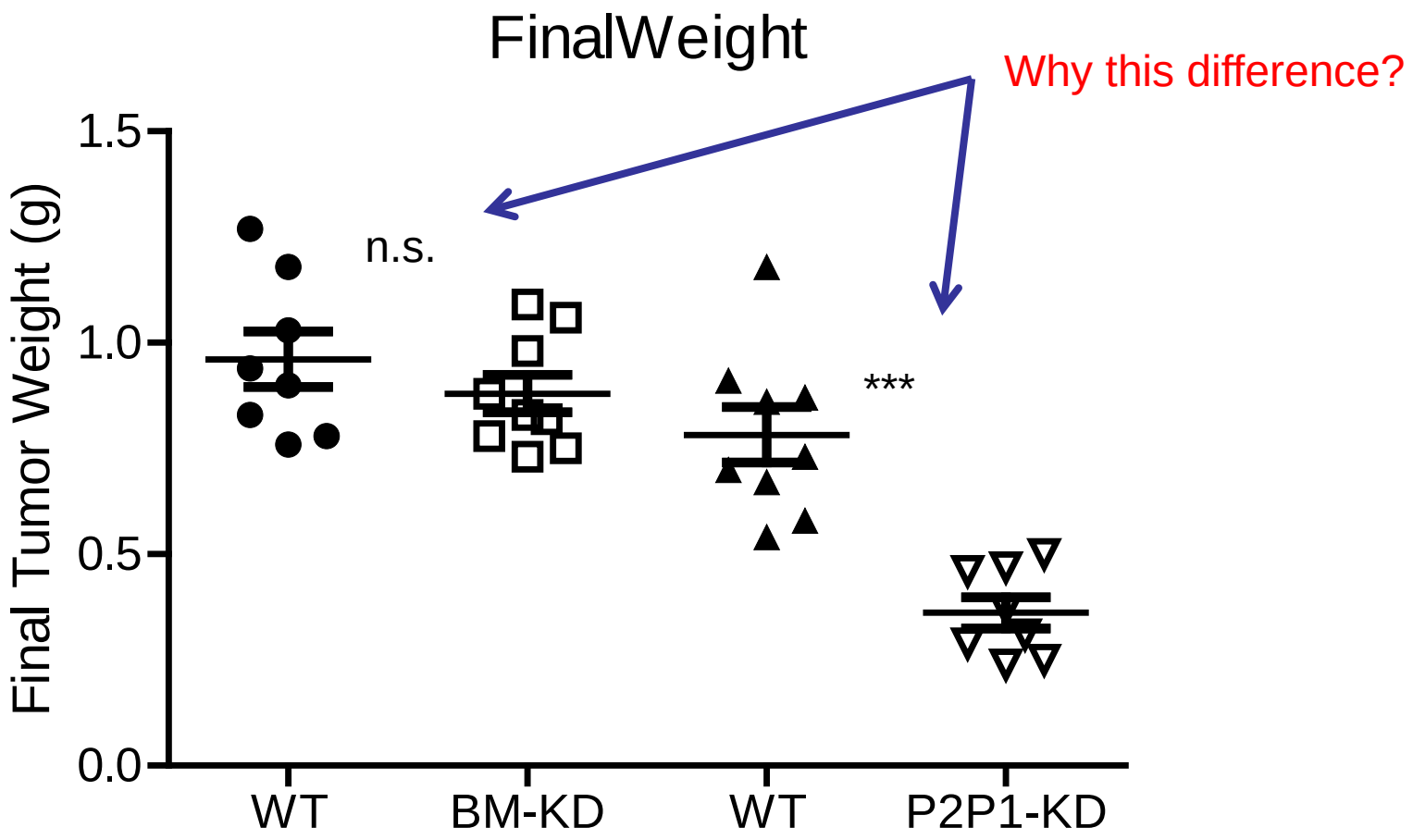




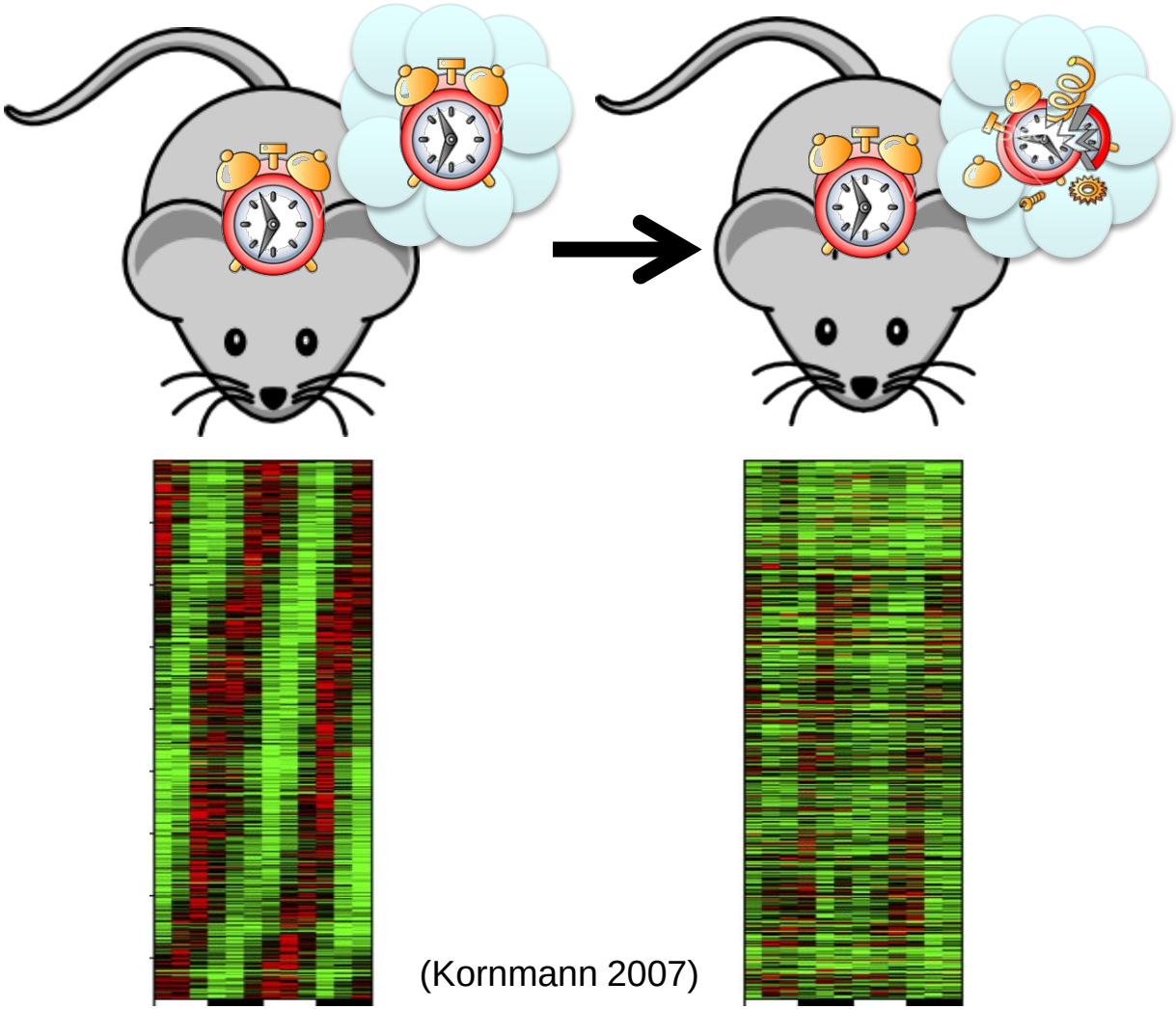
Breaking the clock in C26 in 2 ways



Breaking the clock in C26 in 2 ways

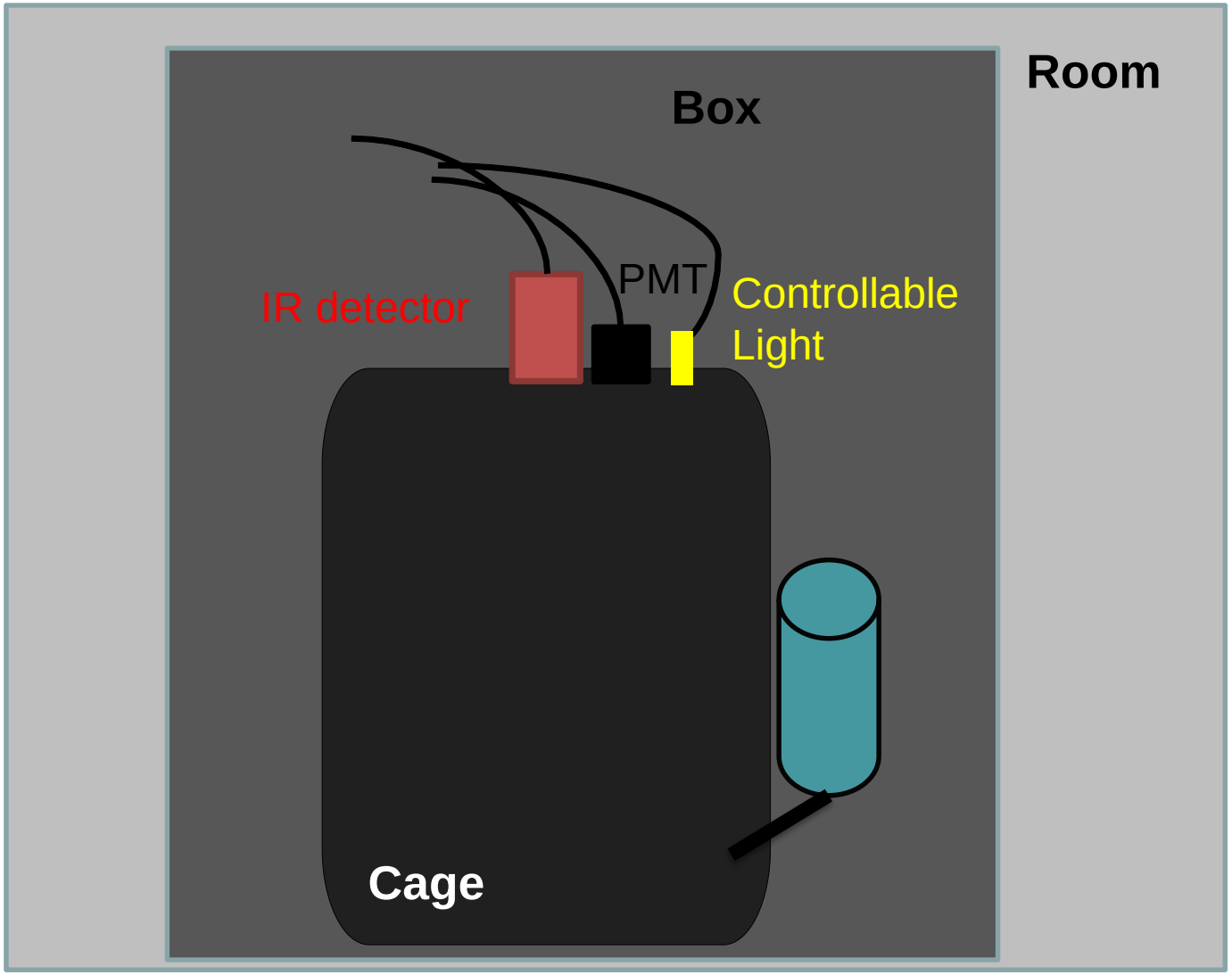


Hypothesis: maybe clock function is being systemically driven here.



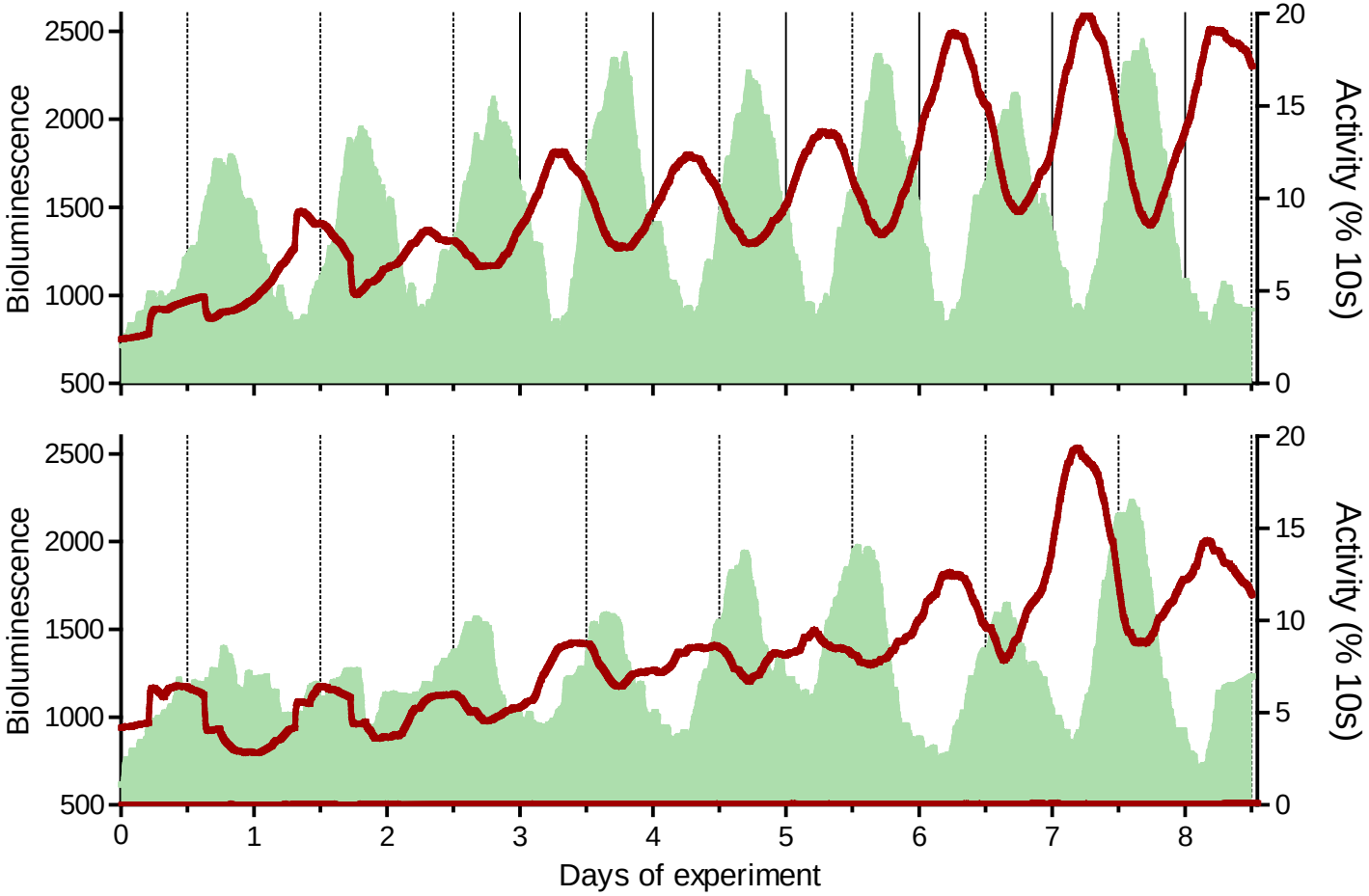
(Kornmann 2007)

In vivo luminometry- principle

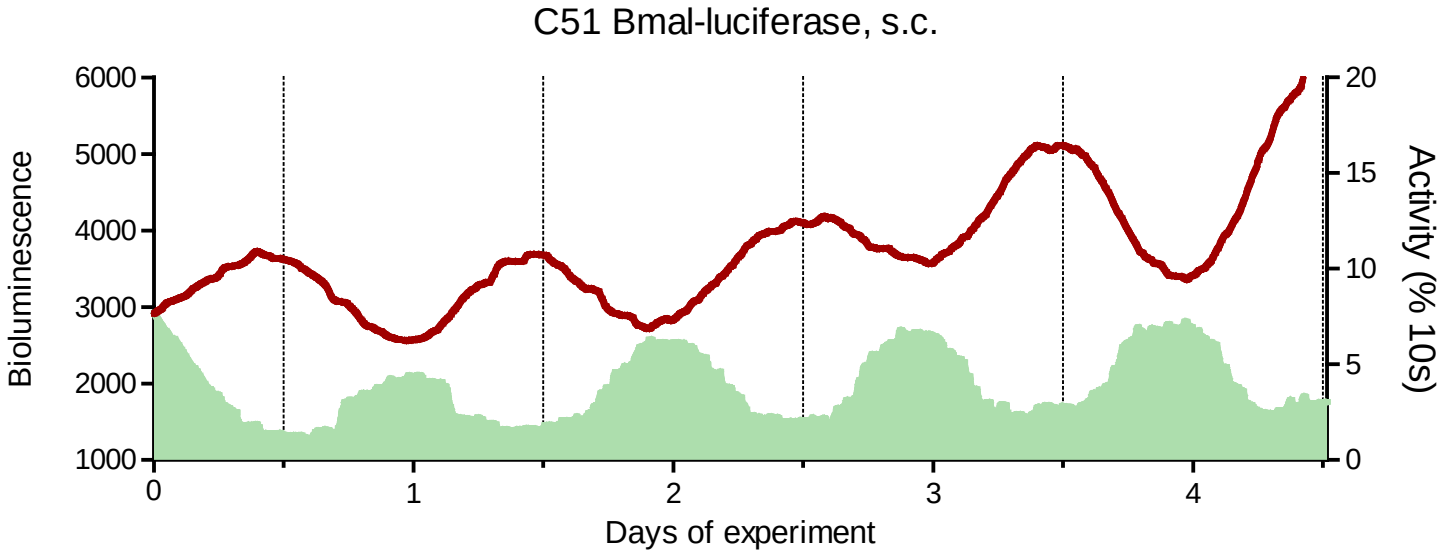


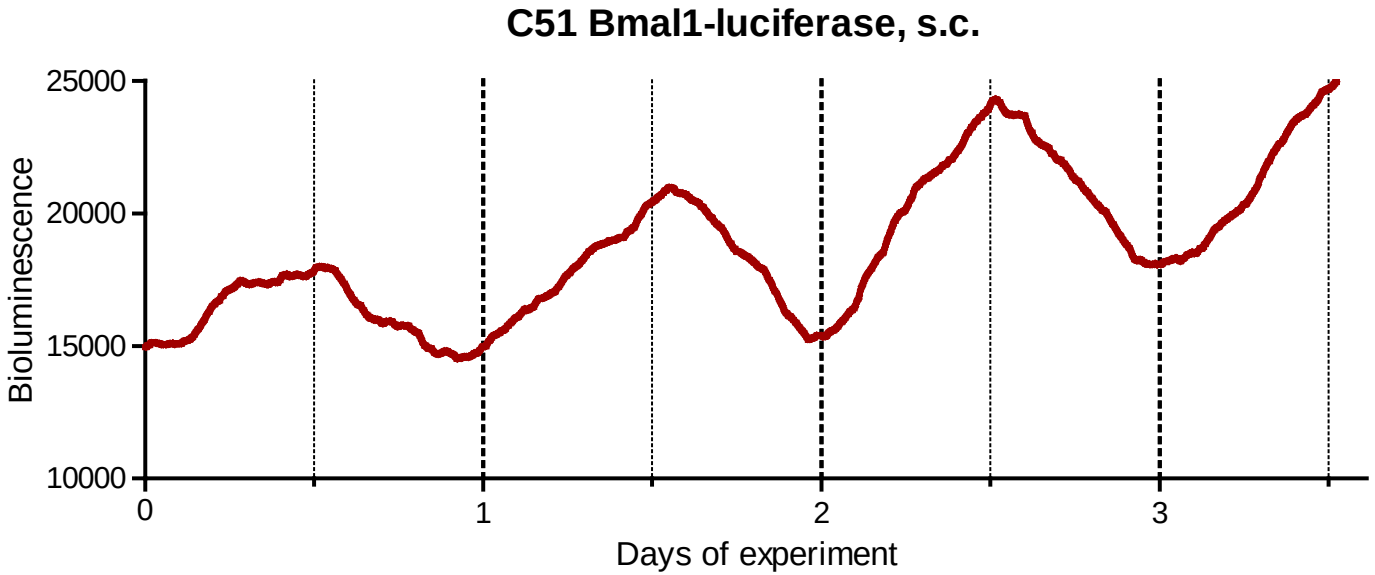
(Saini, 2013)

Rhythmic tumor: Bmal-luciferase in vivo

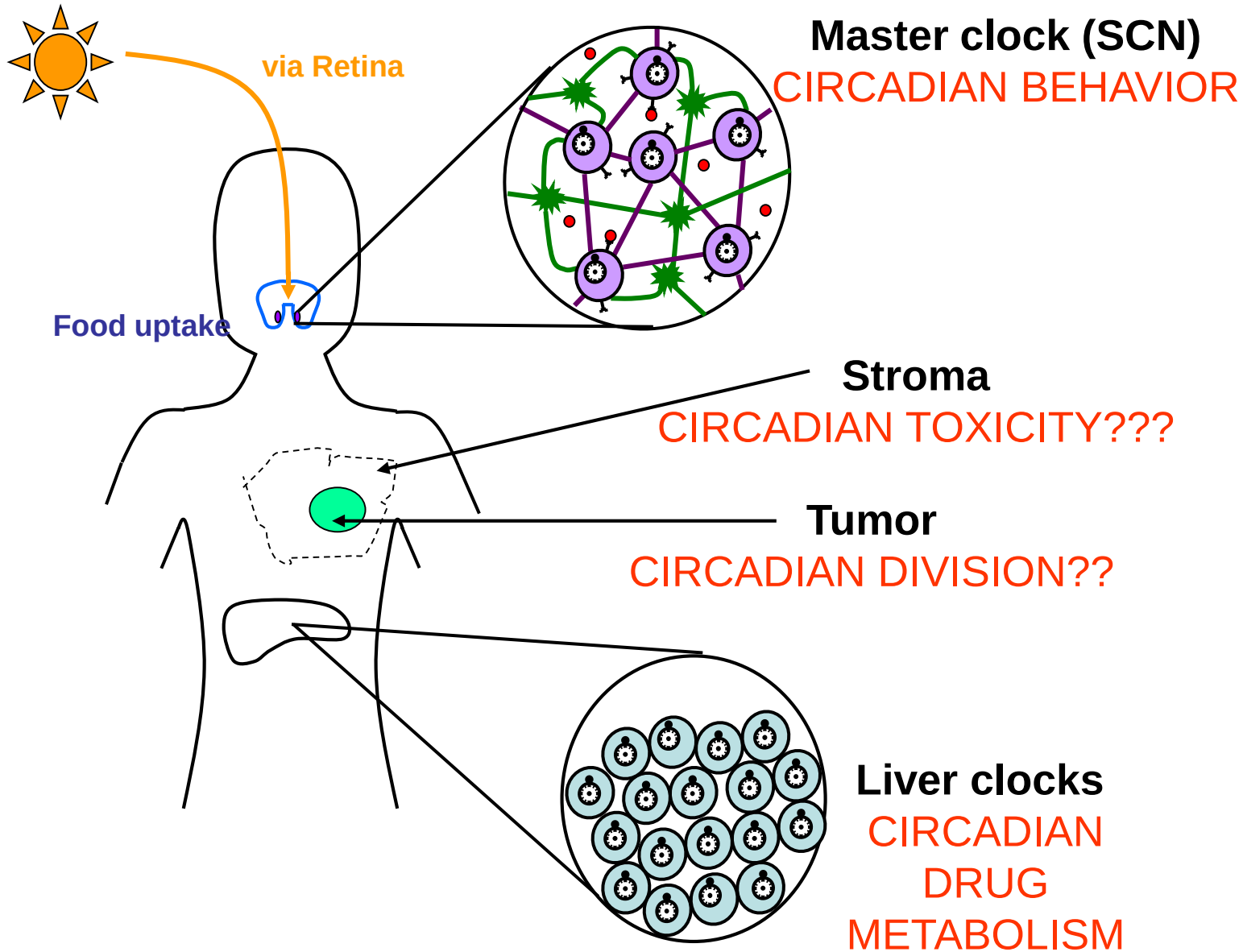


Arrhythmic tumor: Bmal-luciferase in vivo





Conclusions: A four-clock problem?



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