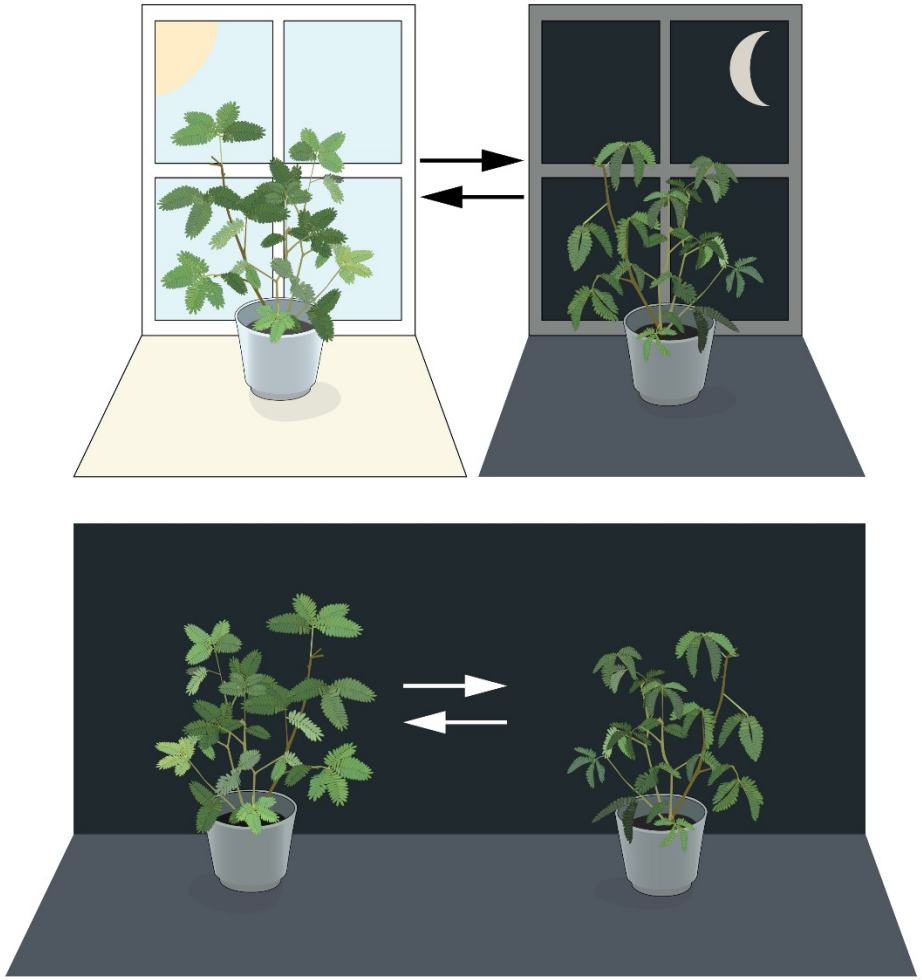
Introduction to translational research

From bench to bedside and back

By Solomon Nshemere

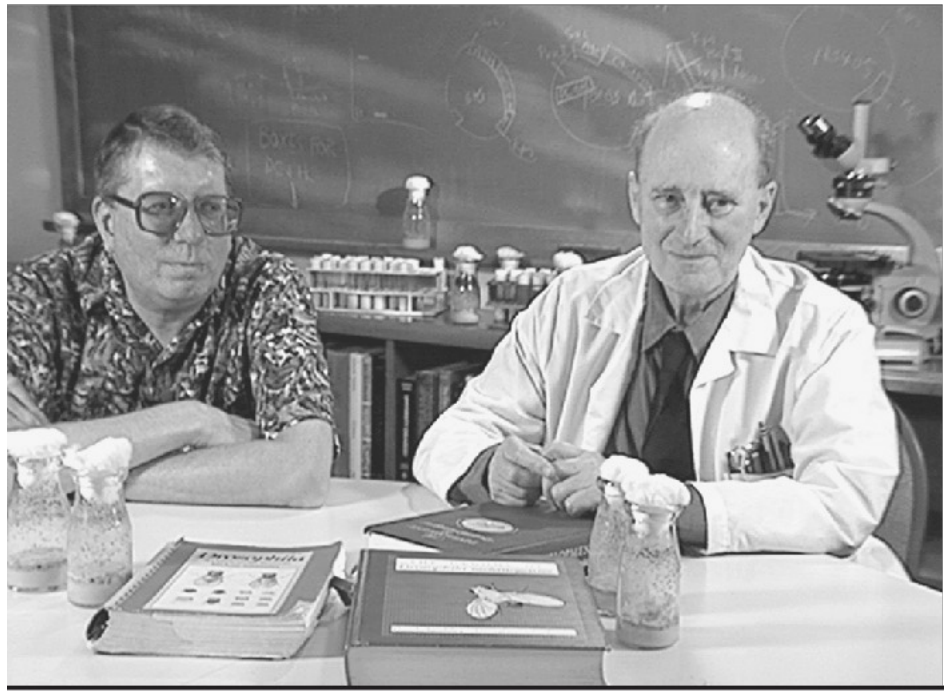
First observation of chronobiology in plants



Jacques d'Ortous de Mairan

The Nobel Assembly press release 2017

Discovery of drosophila mutants with disrupted circadian rythms



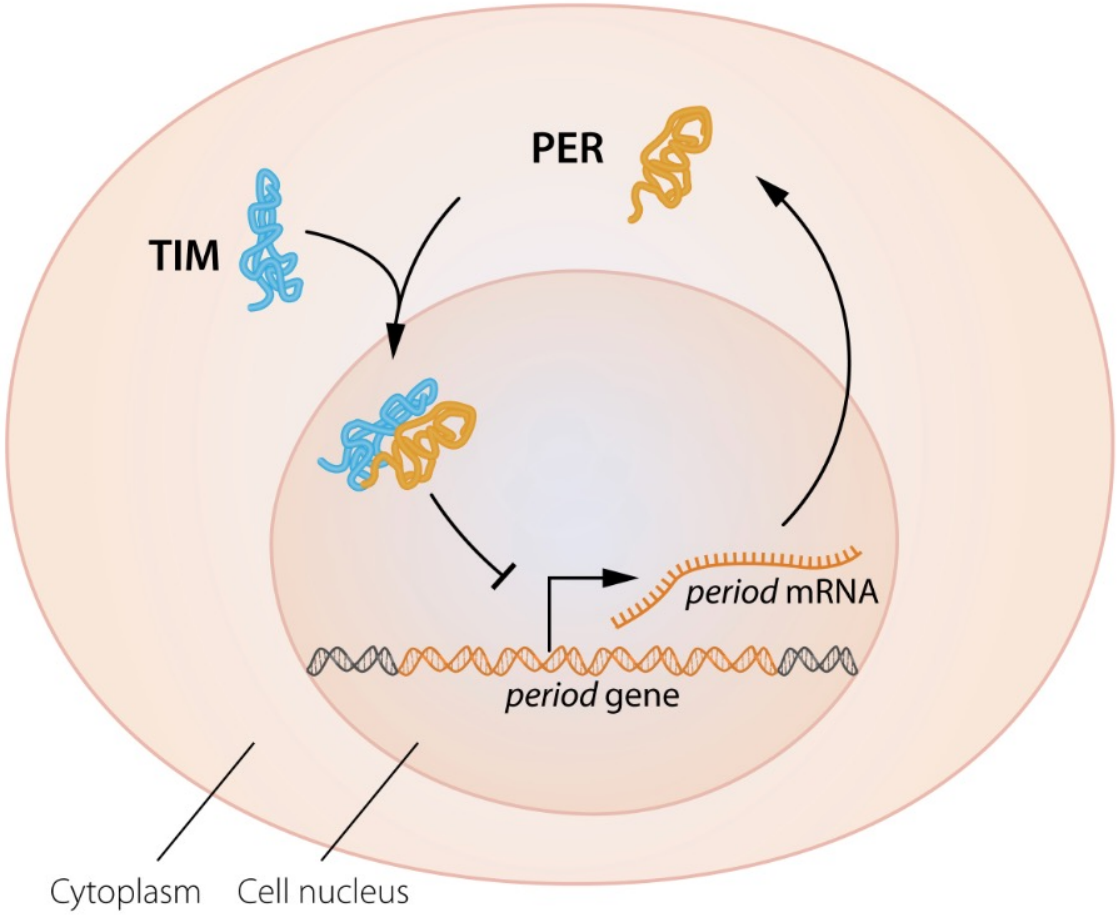
During the 1970's, **Seymour Benzer** and his student **Ronald Konopka** asked whether it would be possible to identify genes that control the circadian rhythm in fruit flies. They demonstrated that mutations in an unknown gene disrupted the circadian clock of flies. They named this gene *period*

The Nobel Assembly press release 2017

Isolation of genes responsible for drosophila circadian biology



In 1984, **Jeffrey Hall** and **Michael Rosbash**, working in close collaboration at Brandeis University in Boston, and **Michael Young** at the Rockefeller University in New York, succeeded in isolating the *period* gene. Jeffrey Hall and Michael Rosbash then went on to discover that PER, the protein encoded by *period,* accumulated during the night and was degraded during the day. Thus, PER protein levels oscillate over a 24-hour cycle, in synchrony with the circadian rhythm



The Nobel Assembly press release 2017

Nobel Prize in Physiology or Medicine 2017

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Jeffrey C. Hall

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Michael Rosbash

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Michael W. Young

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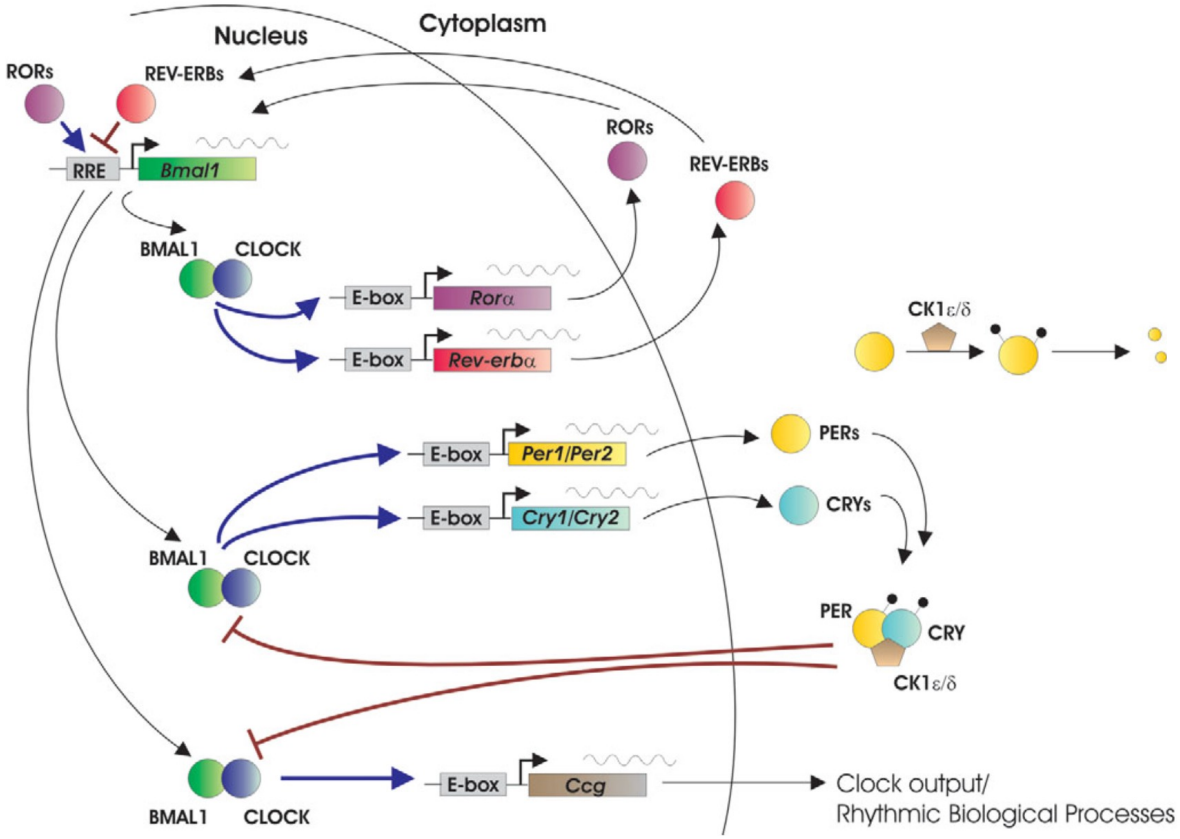
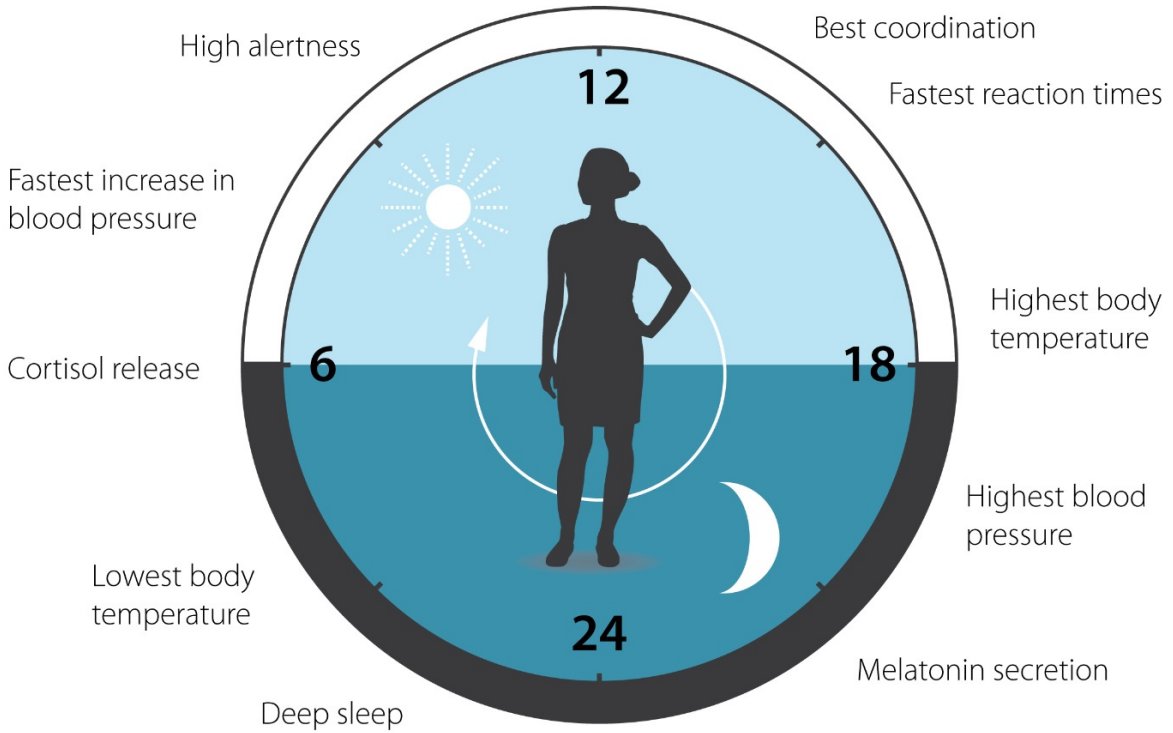
The circadian cock in humans has since been ellucidated and plays important roles in human physiology and pathophysiology

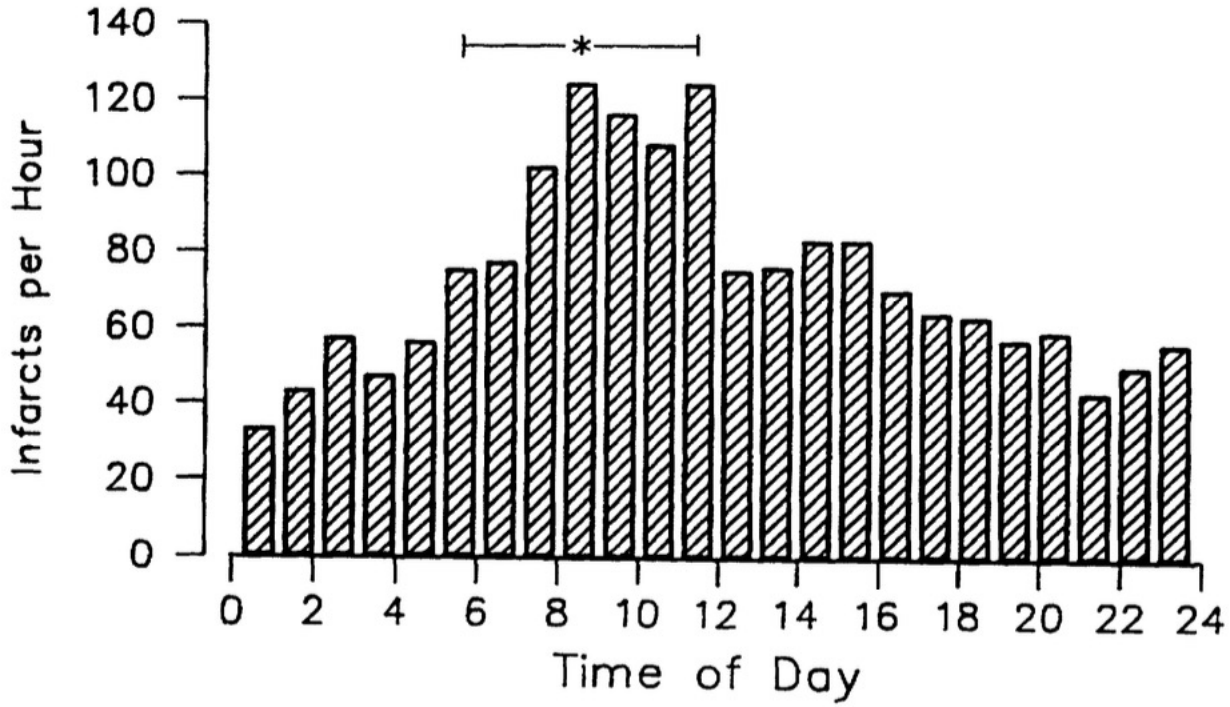




Utpal et al, Sleep medicine 2017

Myocardial Infarctions show a clear circadian pattern

1, 741 patients



Willich et al, Circulation Vol 80, No 4, October 1989

Translating basic research into the clinic

BMAL1–HIF2A heterodimer modulates circadian variations of myocardial injury

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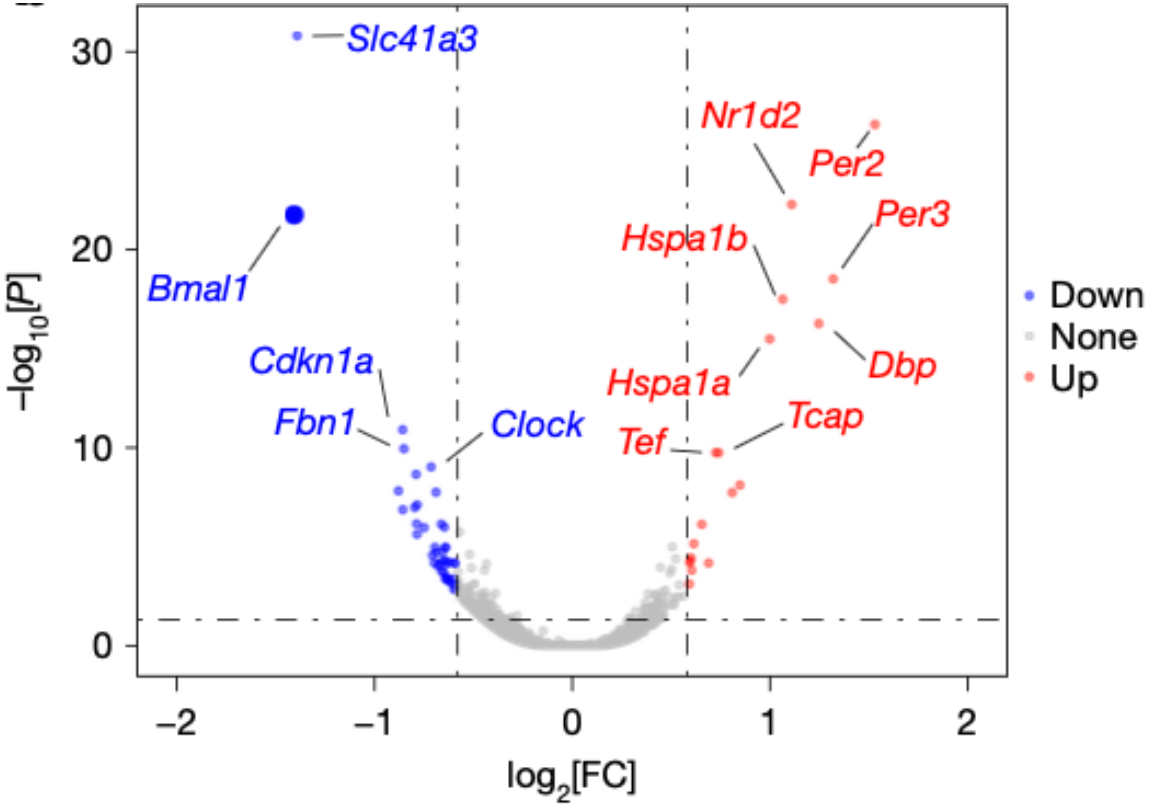
Wei Ruan[1,2,18]✉, Tao Li[3,18], In Hyuk Bang[1,18], Jaewoong Lee[4,18], Wankun Deng[5], Xinxin Ma[1], Cong Luo[1,2], Fang Du[1,6], Seung-Hee Yoo[3], Boyun Kim[1,7], Jiwen Li[1,8], Xiaoyi Yuan[1], Katherine Figarella[1], Yu A. An[1], Yin-Ying Wang[5], Yafen Liang[1,9], Matthew DeBerge[1], Dongze Zhang[1], Zhen Zhou[10], Yanyu Wang[1], Joshua M. Gorham[11], Jonathan G. Seidman[11], Christine E. Seidman[11], Sary F. Aranki[12], Ragini Nair[1], Lei Li[13], Jagat Narula[14], Zhongming Zhao[5], Alemayehu A. Gorfe[15], Jochen D. Muehlschlegel[16], Kuang-Lei Tsai[3,17]✉ & Holger K. Eltzschig[1,9]✉

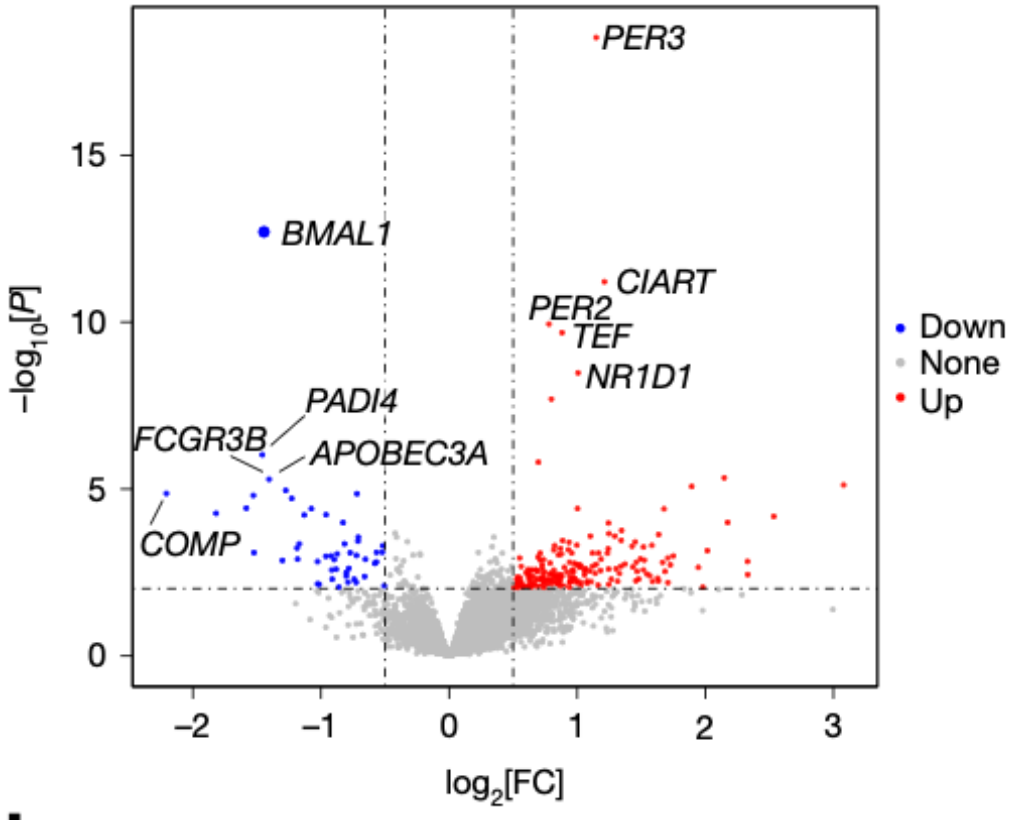
Acute myocardial infarction is a leading cause of morbidity and mortality worldwide[1]. Clinical studies have shown that the severity of cardiac injury after myocardial infarction exhibits a circadian pattern, with larger infarcts and poorer outcomes in patients experiencing morning-onset events[2–7]. However, the molecular mechanisms underlying these diurnal variations remain unclear. Here we show that the core circadian transcription factor BMAL1[7–11] regulates circadian-dependent myocardial injury by forming a transcriptionally active heterodimer with a non-canonical partner—hypoxia-inducible factor 2 alpha (HIF2A)[12–16]—in a diurnal manner. To substantiate this finding, we determined the cryo-EM structure of the BMAL1–HIF2A–DNA complex, revealing structural rearrangements within BMAL1 that enable cross-talk between circadian rhythms and hypoxia signalling. BMAL1 modulates the circadian hypoxic response by enhancing the transcriptional activity of HIF2A and stabilizing the HIF2A protein. We further identified amphiregulin (AREG)[16,17] as a rhythmic target of the BMAL1–HIF2A complex, critical for regulating daytime variations of myocardial injury. Pharmacologically targeting the BMAL1–HIF2A–AREG pathway provides cardioprotection, with maximum efficacy when aligned with the pathway's circadian phase. These findings identify a mechanism governing circadian

Ruan, W., Li, T., Bang, I.H. *et al.* BMAL1–HIF2A heterodimer modulates circadian variations of myocardial injury. *Nature* **641**, 1017–1028 (2025)

Mouse models can recapitulate circadian rhythms observed in humans

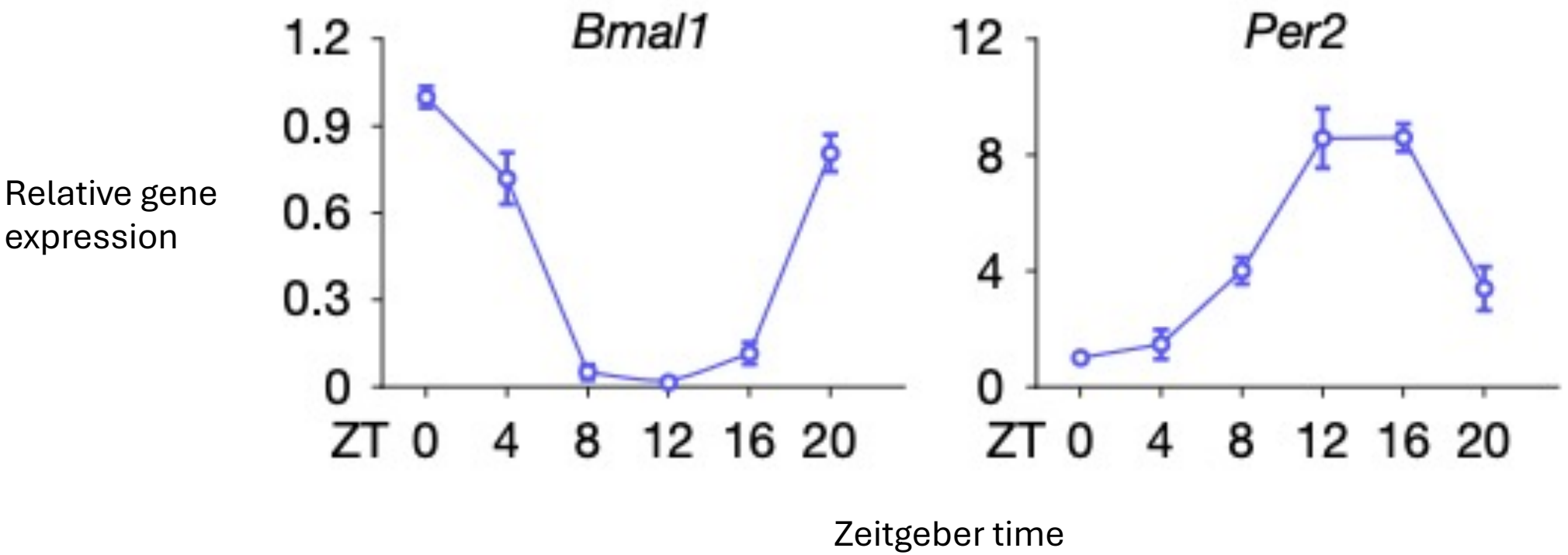


RNA seq of AAR samples taken from mice at ZT8 when MI is least prominent

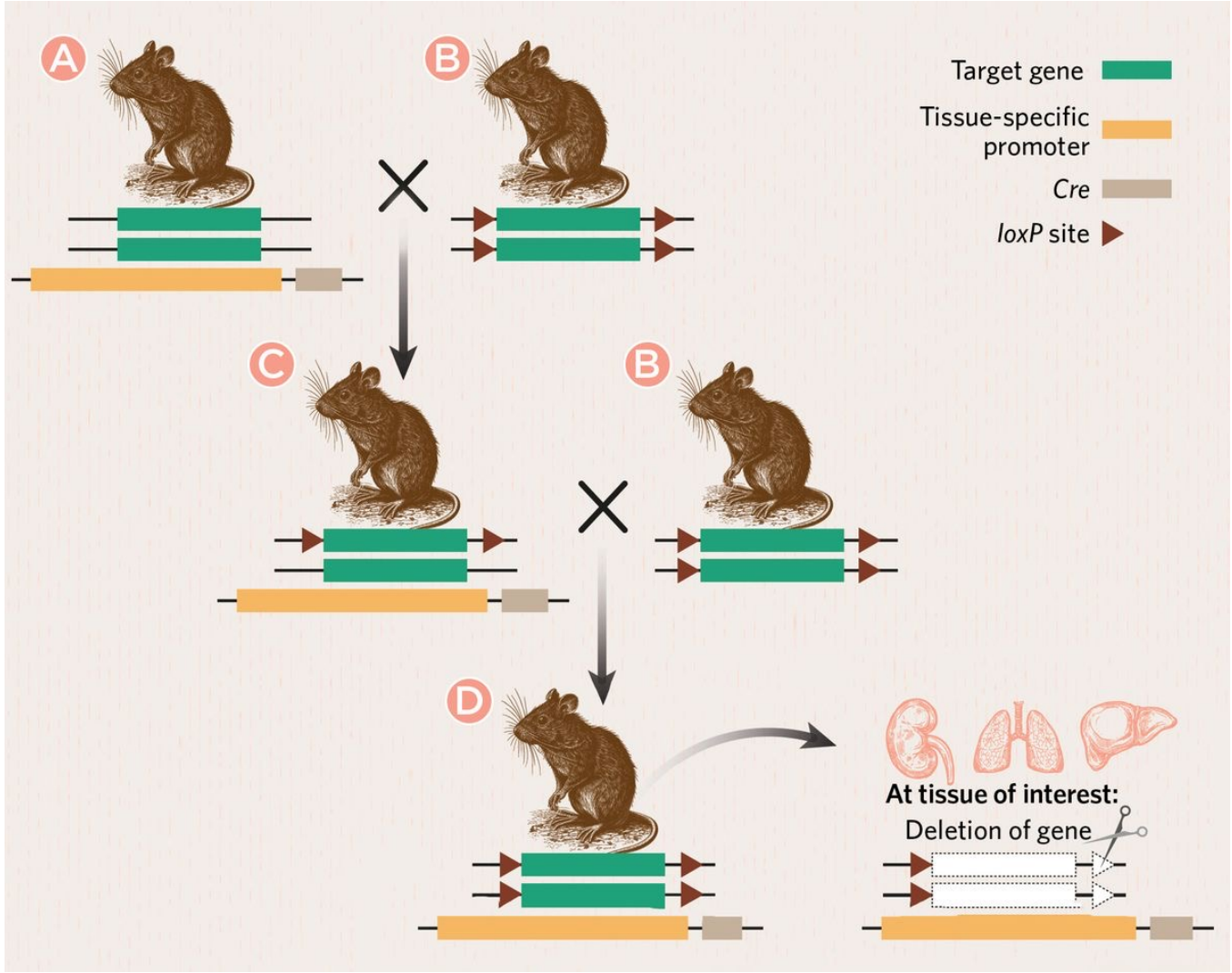


RNA seq of ischemic patient samples taken in the morning (10:32 am)

Bmal1 and Per2 show cicadian patterns in mice similar to humans



Generation of transgenic mice to investigate Bmal1's funtional role in cardiac injury



Bmal1

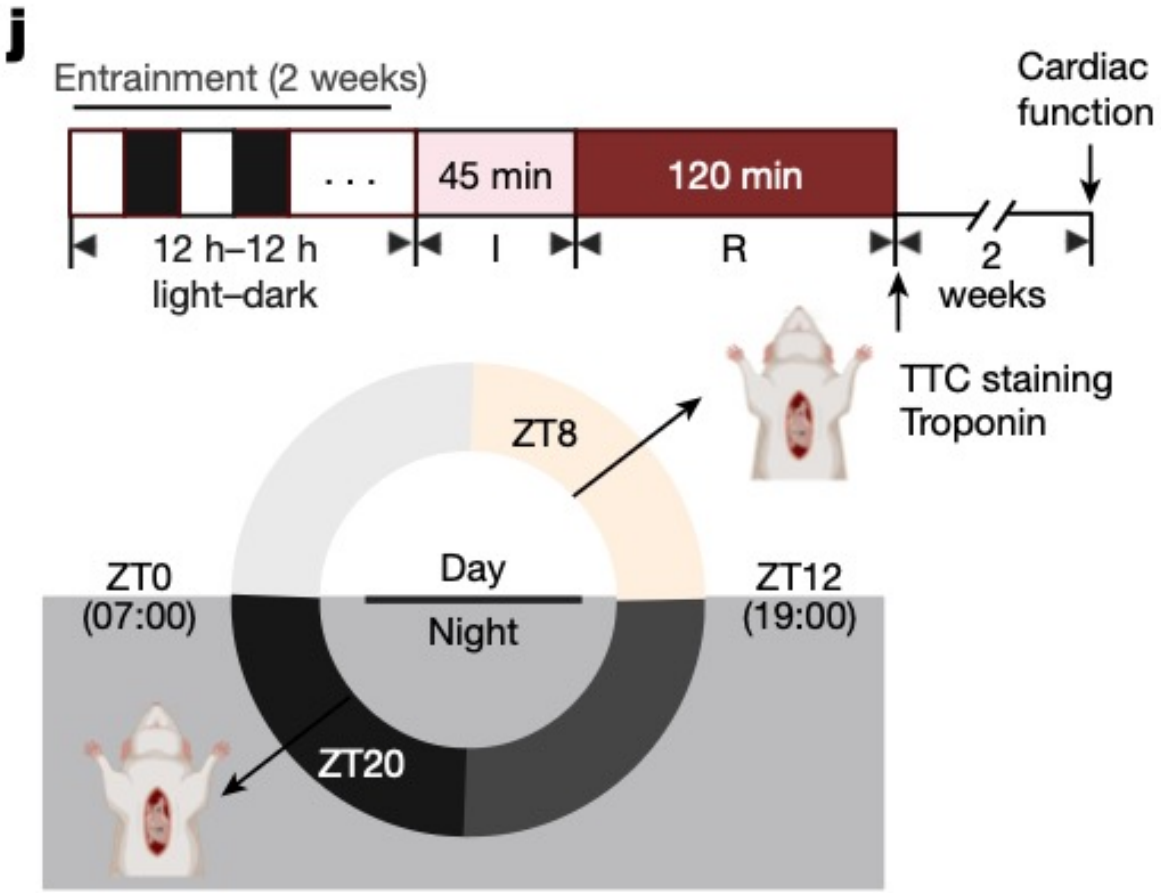
Myh6

Cre recombinase

The result is a mouse model in which tamoxifen injection will induce ablation of Bmal1 specifically in cardiomyocytes

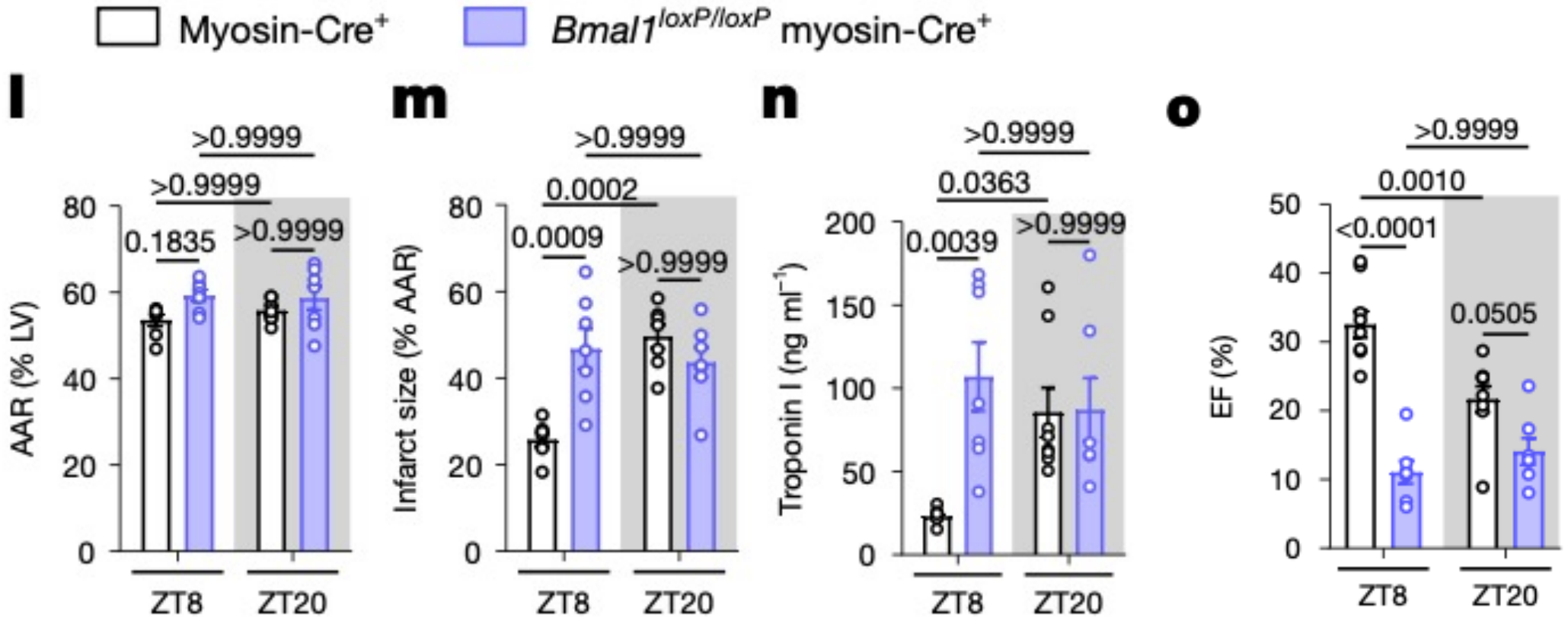
https://www.the-scientist.com/infographic-the-cre-lox-system-explained-71500

Study design



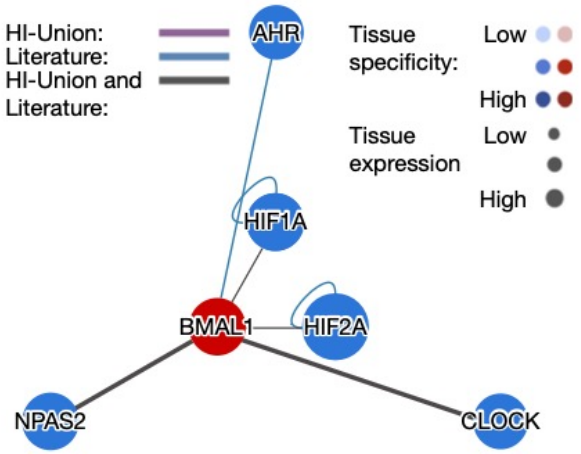
Bmal1 KO mice and Control mice were subjected to MI either at ZT8 or ZT20

Bmal1 regulates circadian cardiac injury

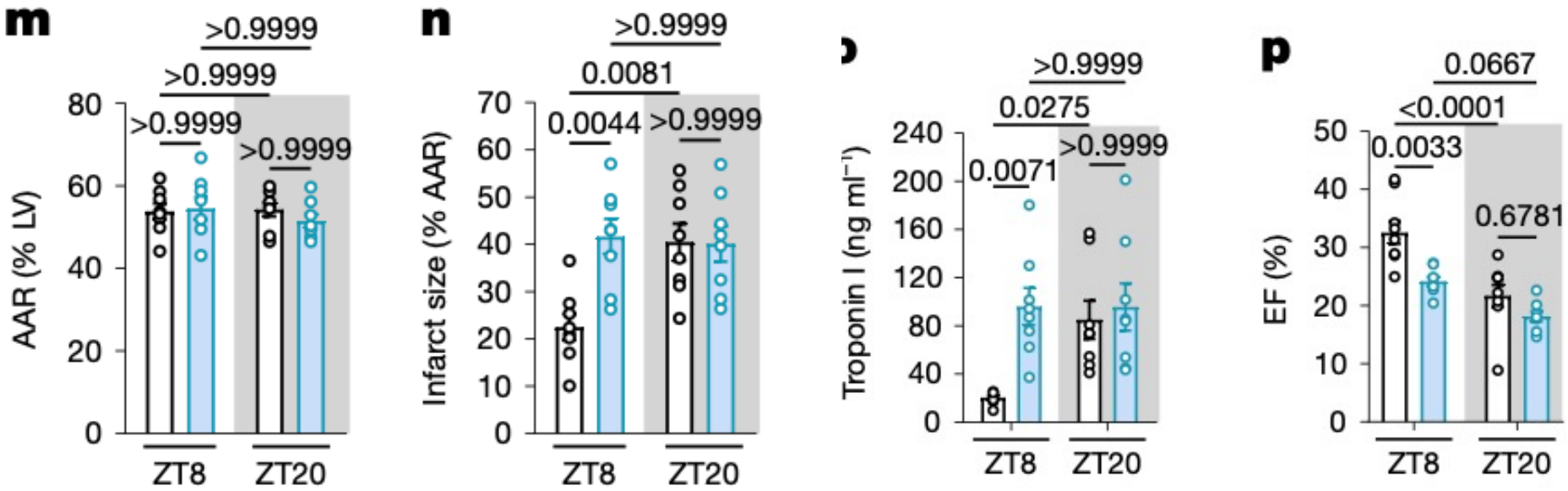


But how does Bmal1 regulate circadian cardiac injury?

Bmal1 interacts with Hif2a to regulate circadian cardiac injury

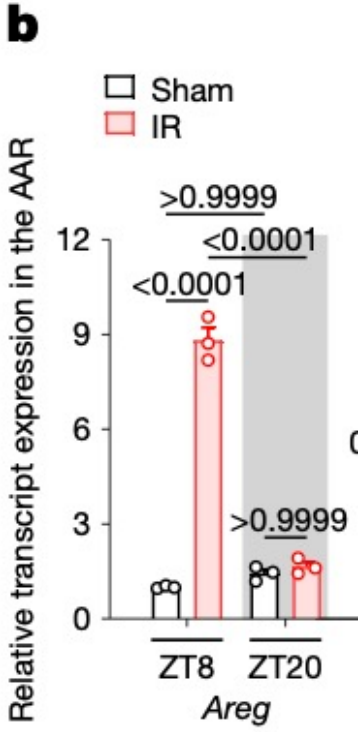


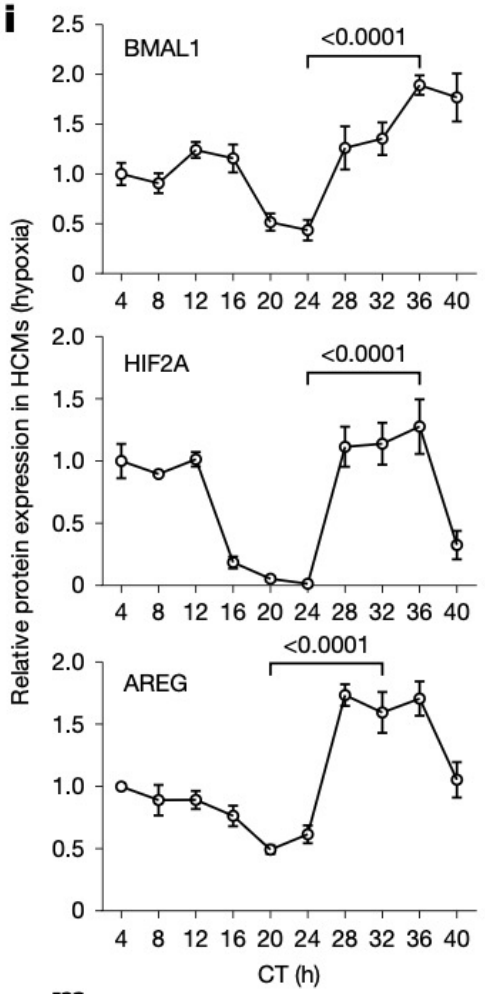
Using Cre-Lox strategy, the authors created a mose model in which **Hif2a is ablated in cardiomyocytes** upon tamoxifen injection



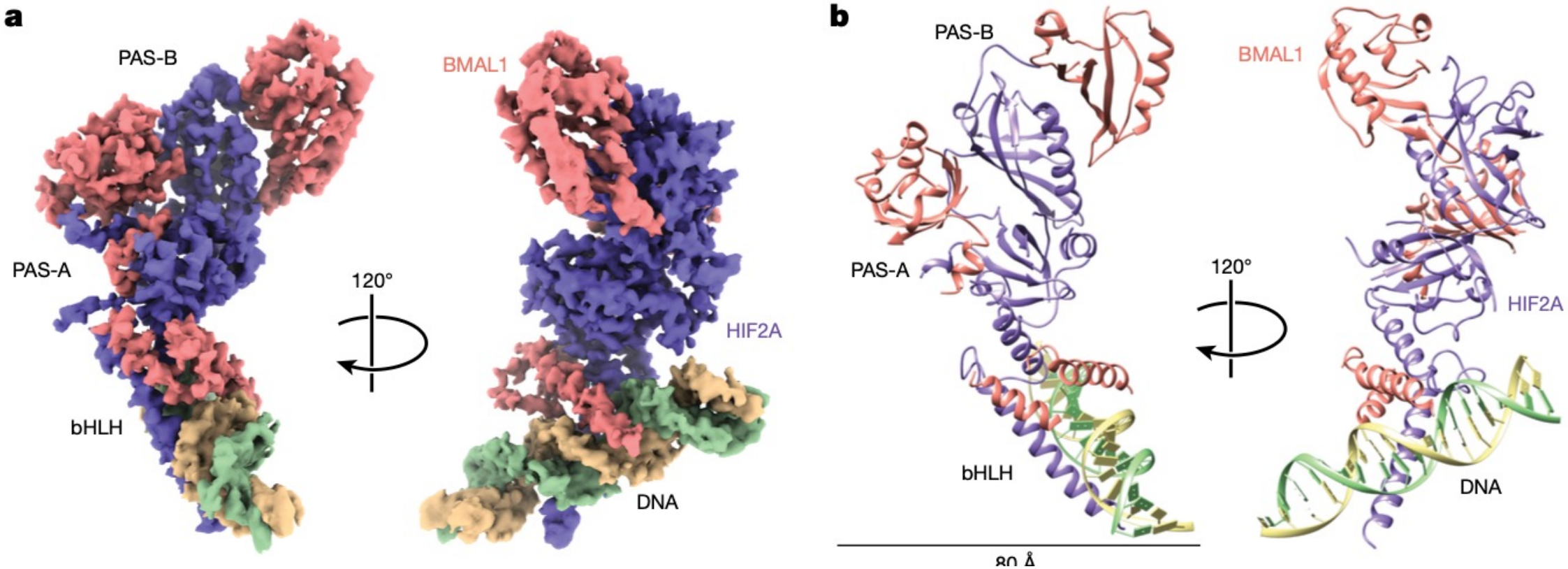
But how does Bmal-Hif2a complex regulate circadian cardiac injury?

Areg is the most significantly upregulated Hif2a target gene after cardiac injury and shows similar circadian patterns

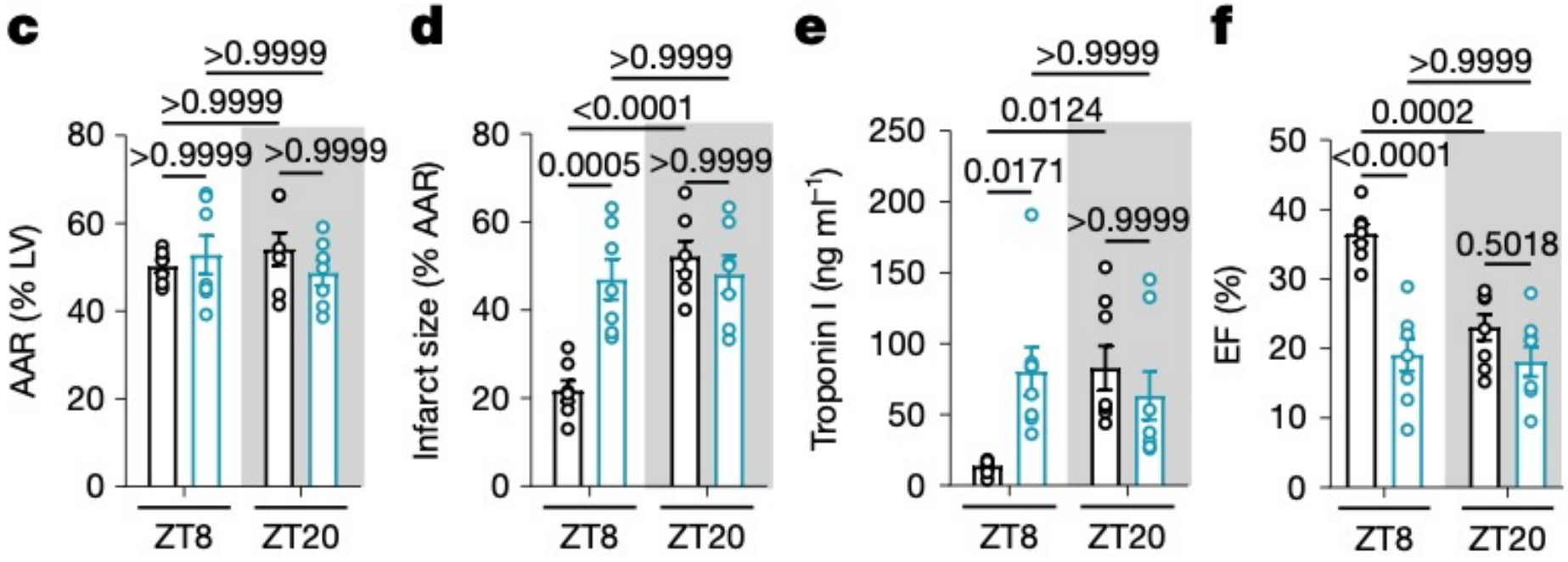




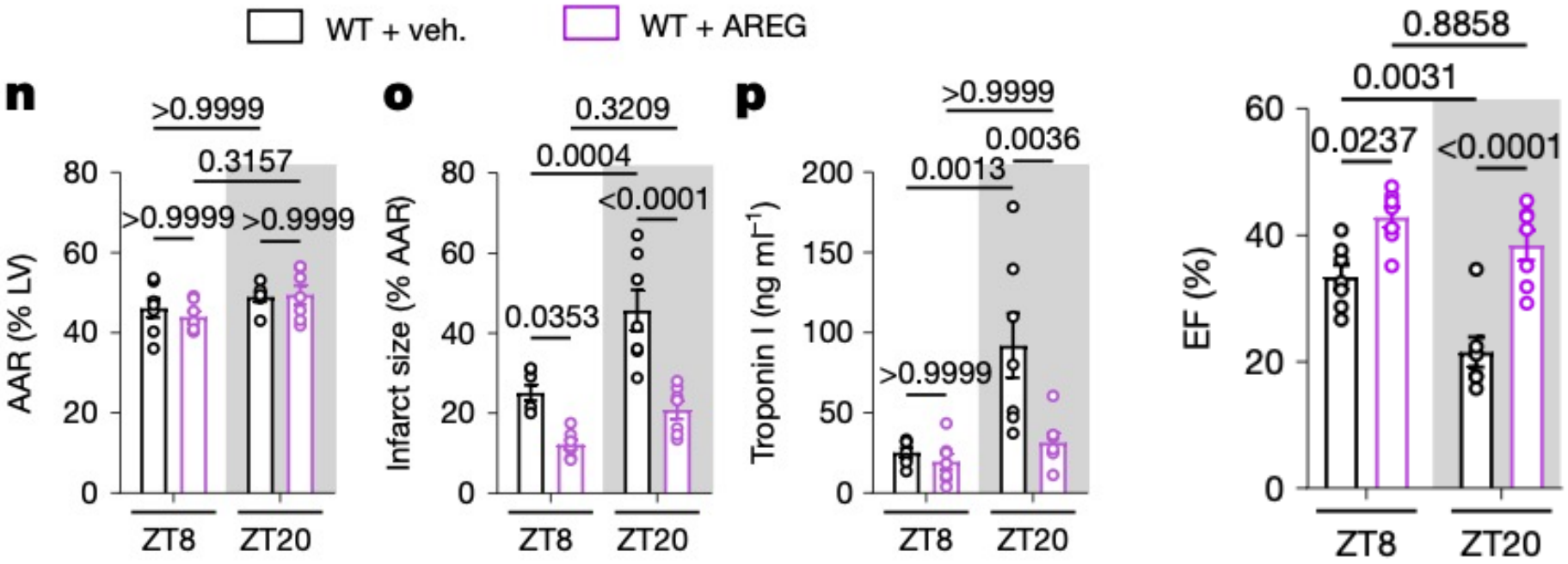
The authors show that Bmal1 dimerizes with Hif2a to drive Areg expression



Areg KO mice exhibit similar characteristics to Bmal1 and Hif2a KO mice



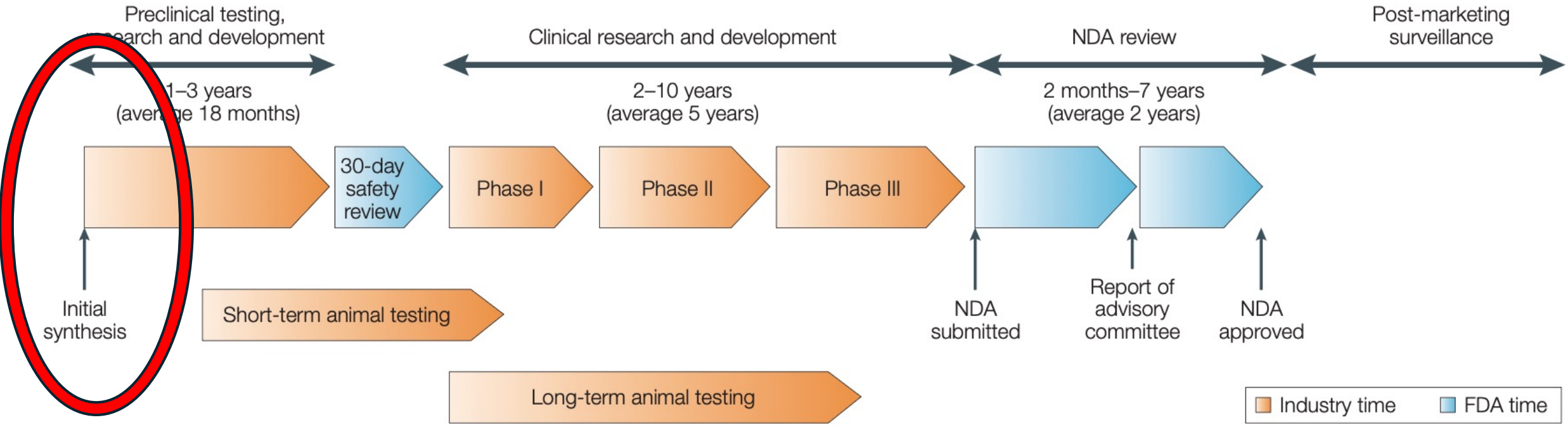
Recombinant Areg as a chronotherapeutic strategy??



Conclusions summary

- The authors ellucidate the mechanism by which **Bmal1 regulates cardiac circadian cycles by interacting with Bmal1 to drive expression of Areg**
- The authors elegantly demonstrate that **targeting the Bmal1-Hif2a-Areg axis could be a potential therapeutic avenue** for myocardial injury

So where does this work place us in the drug development timeline?



Nat Rev Drug Disc 2004; 3: 417-429

Thank you for listening