Oct 10, 2013, JSSX Young Investigator's Award

Chronopharmacokinetic study based on molecular circadian clock

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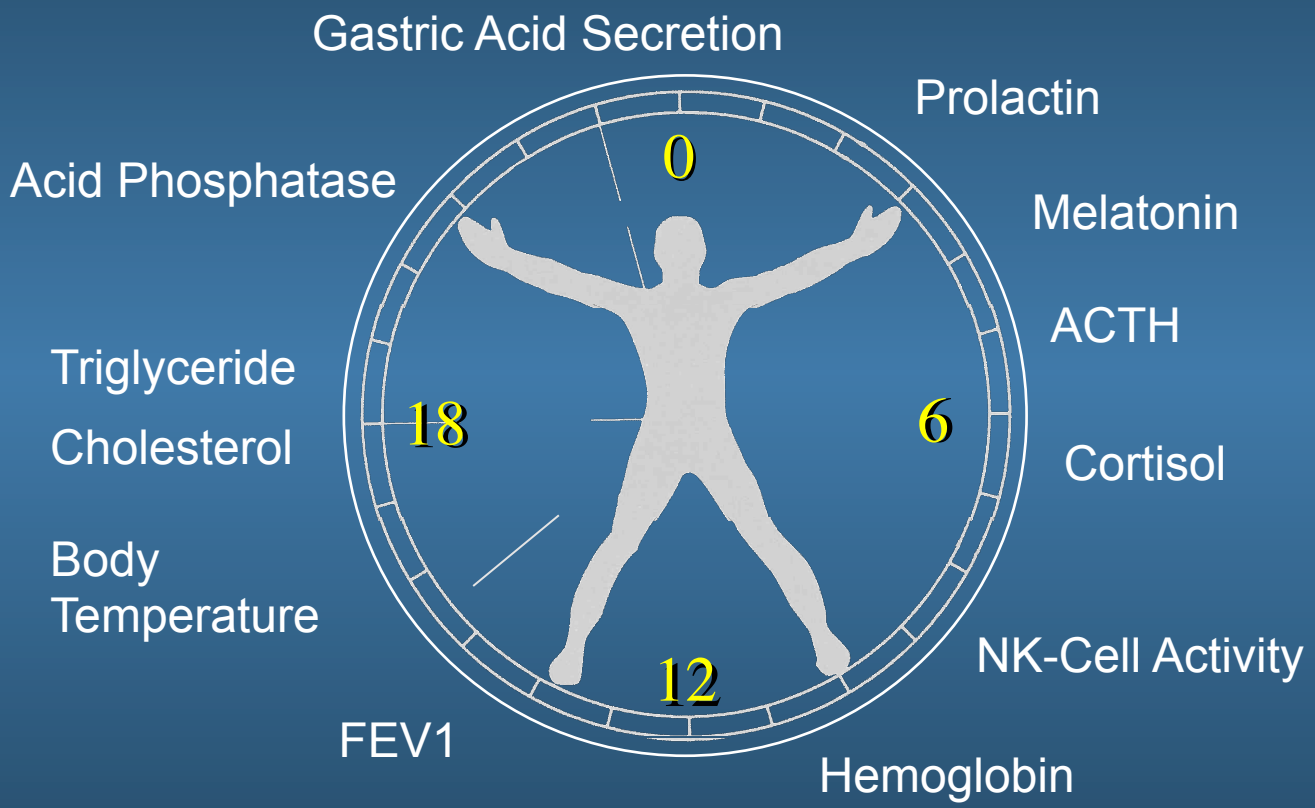
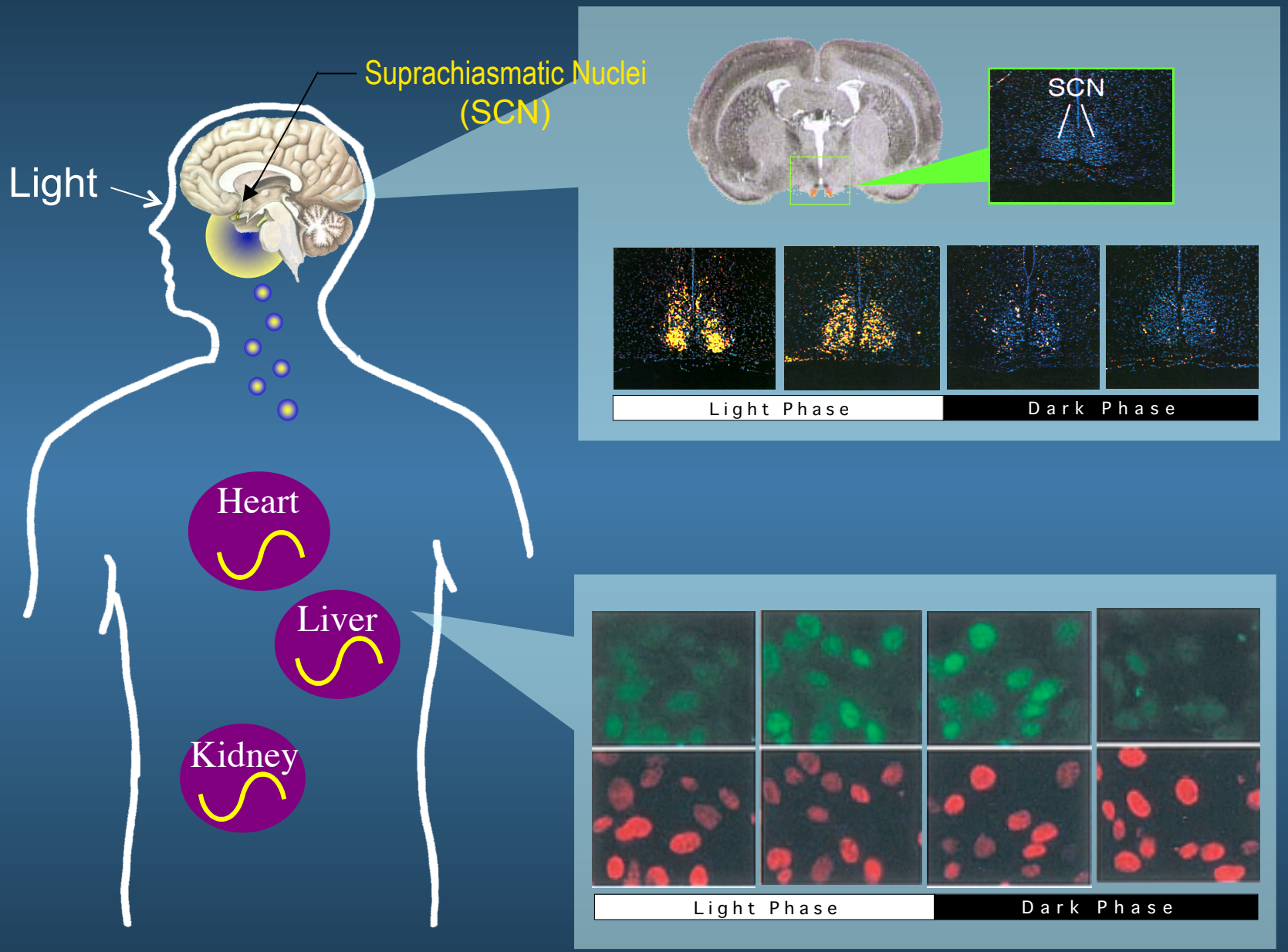
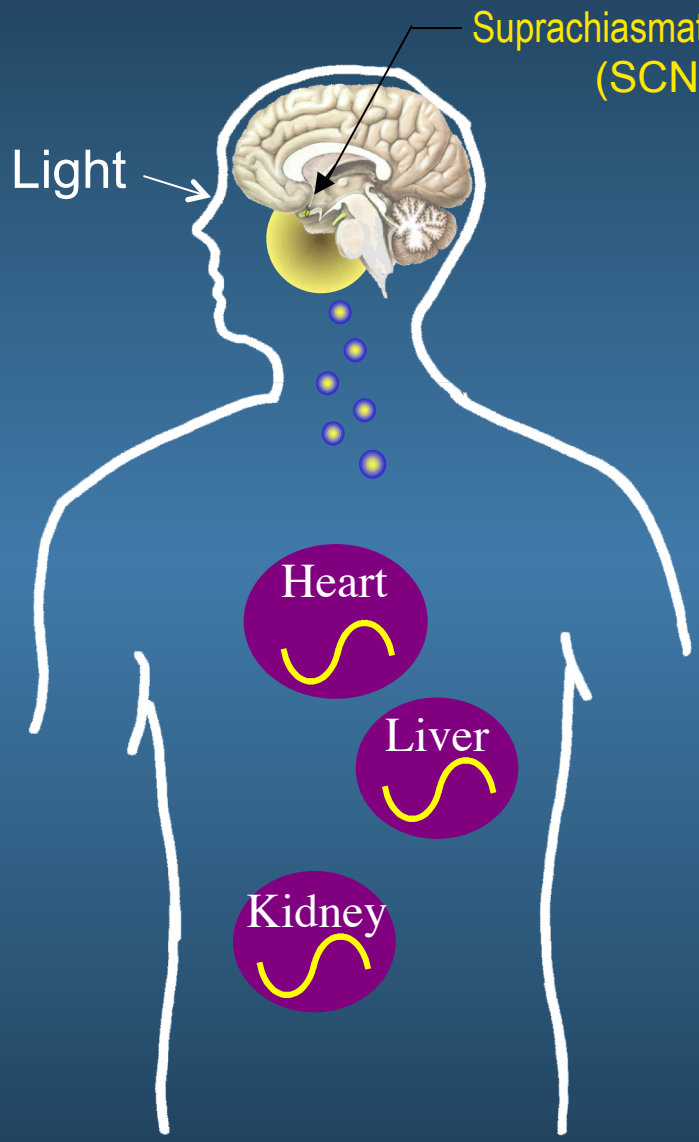
Approximate Peak Time of Physiological or Biochemical Functions in Human Following Dirunal Active / Noctural Sleep



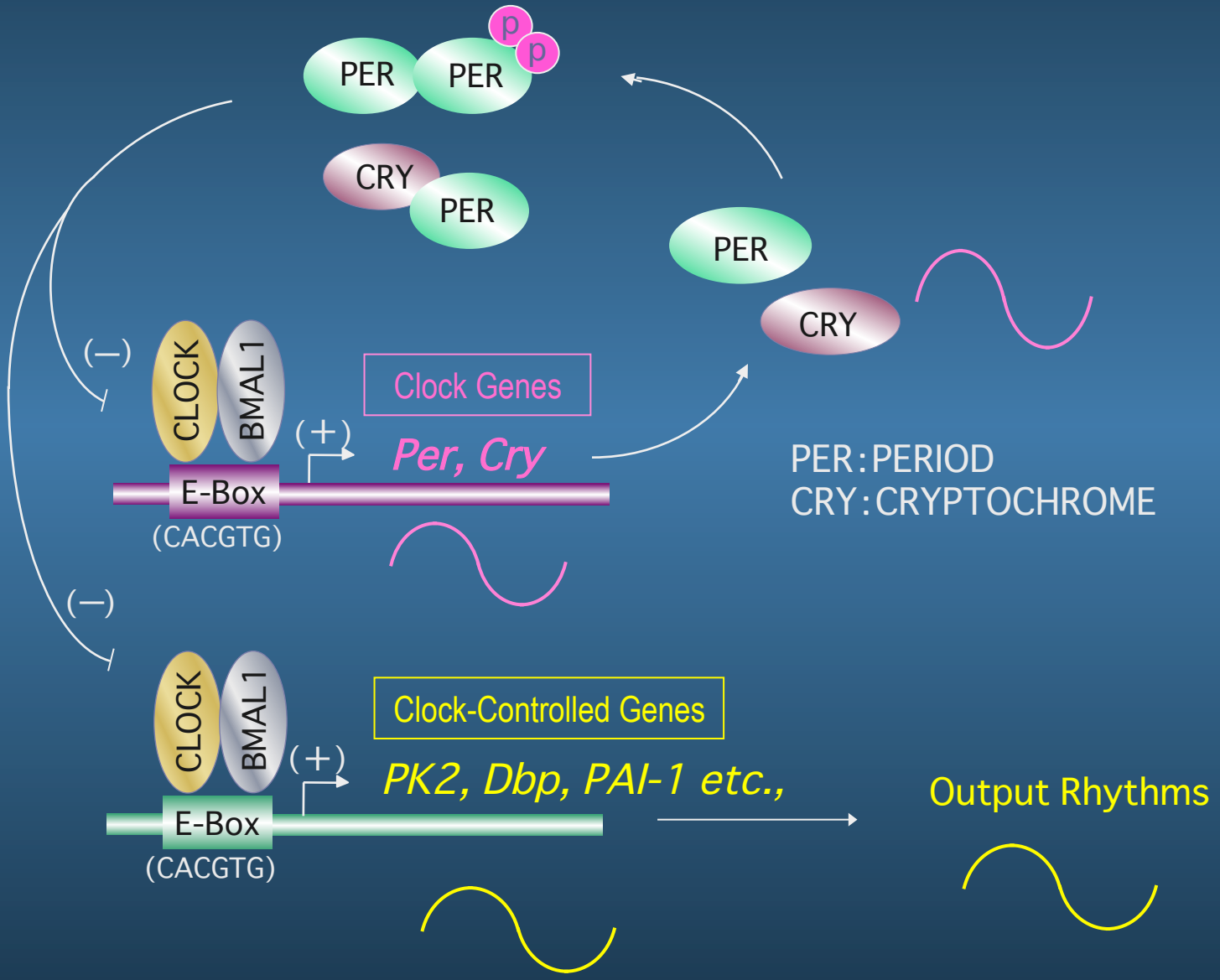

Suprachiasmatic Nuclei
(SCN)
Light
Heart
Liver
Kidney
SCN
Light Phase
Dark Phase
Light Phase
Dark Phase



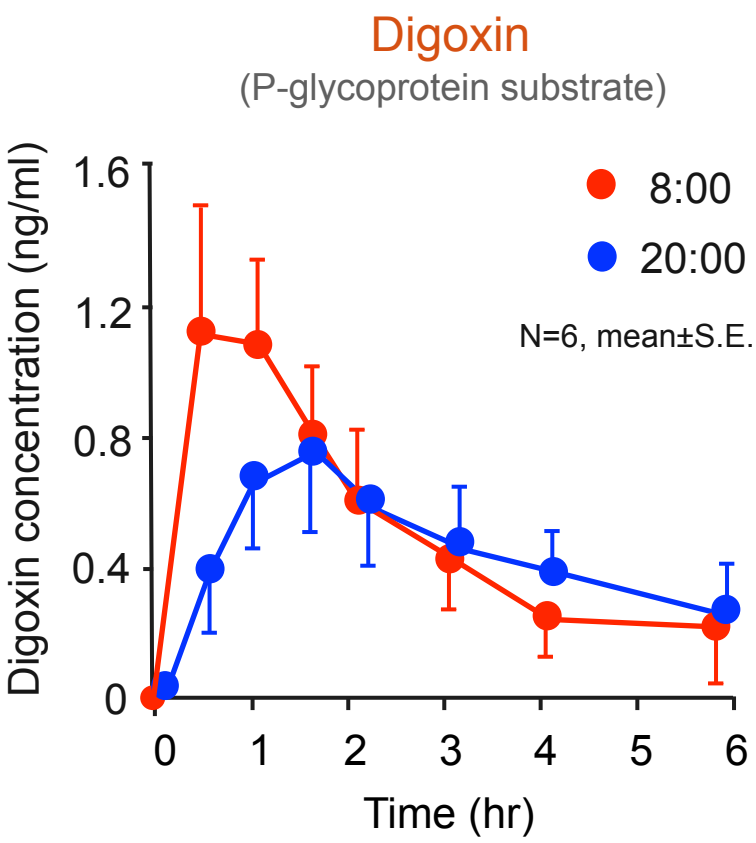
Circadian Clock Genes in Mammals

- Clock (*CLK*, *MOP4*)
- Bmal (*Bmal1*, *Bmal2*)
- Period (*Per1*, *Per2*, *Per3*)
- Cryptochrome (*Cry1*, *Cry2*)
- Rev-erbα ・ROR

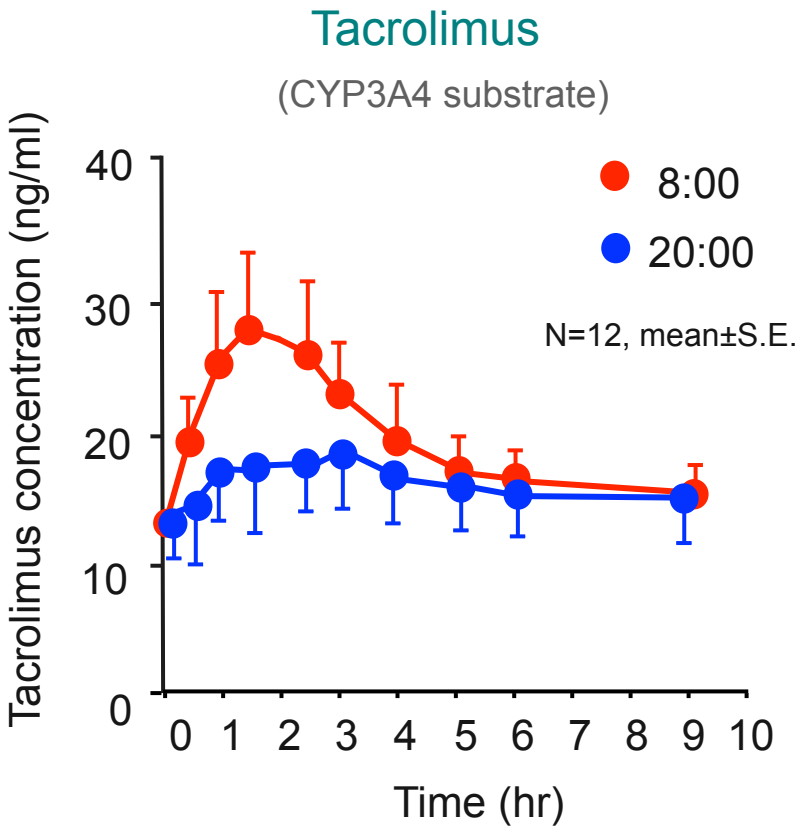
Schematic molecular mechanism of mammalian circadian clock system



Dosing time-dependent changes in the pharmacokinetics of digoxin and tacrolimus in human

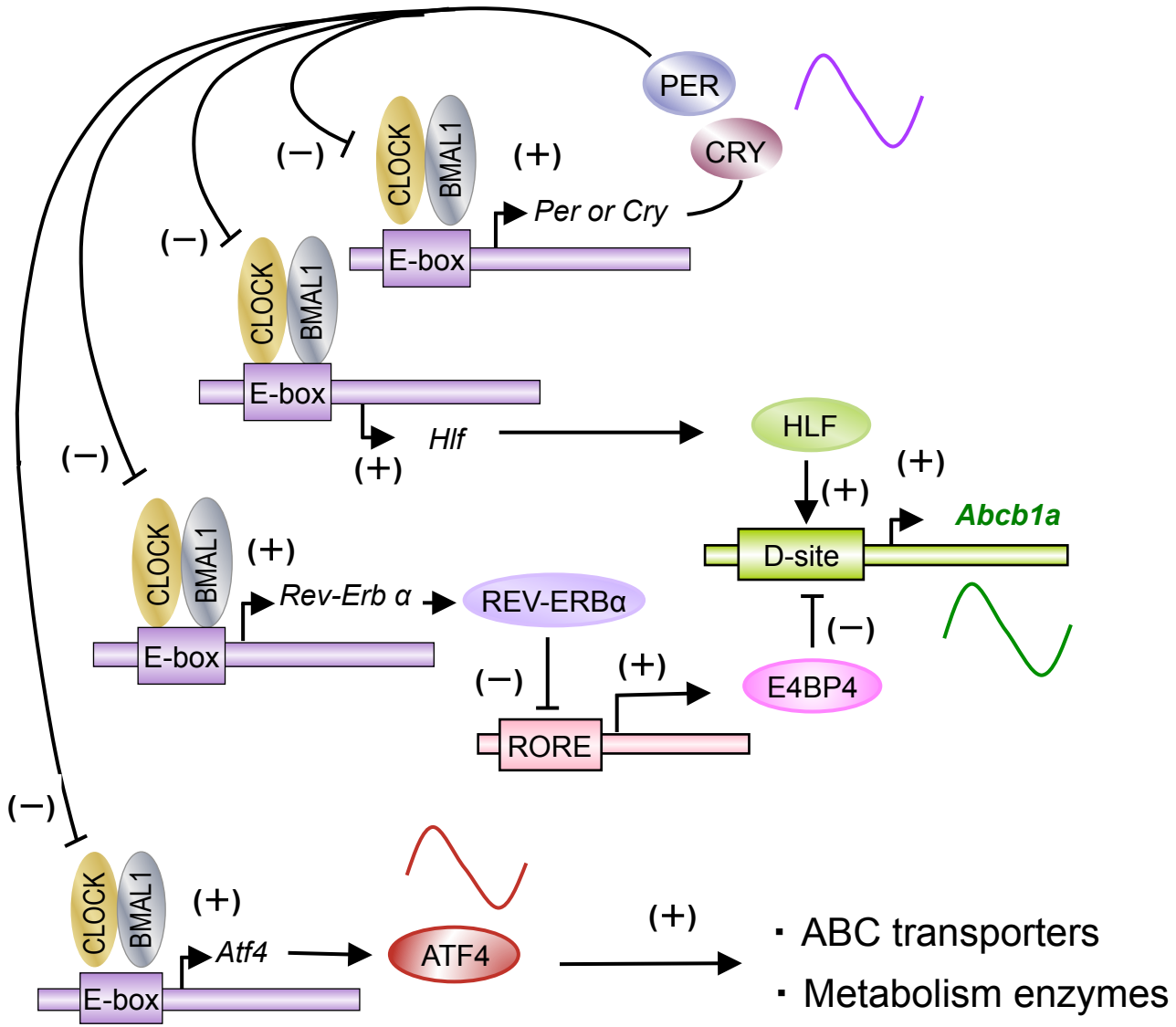


Erol et al., *Chronobiology Int.* 18, 2001



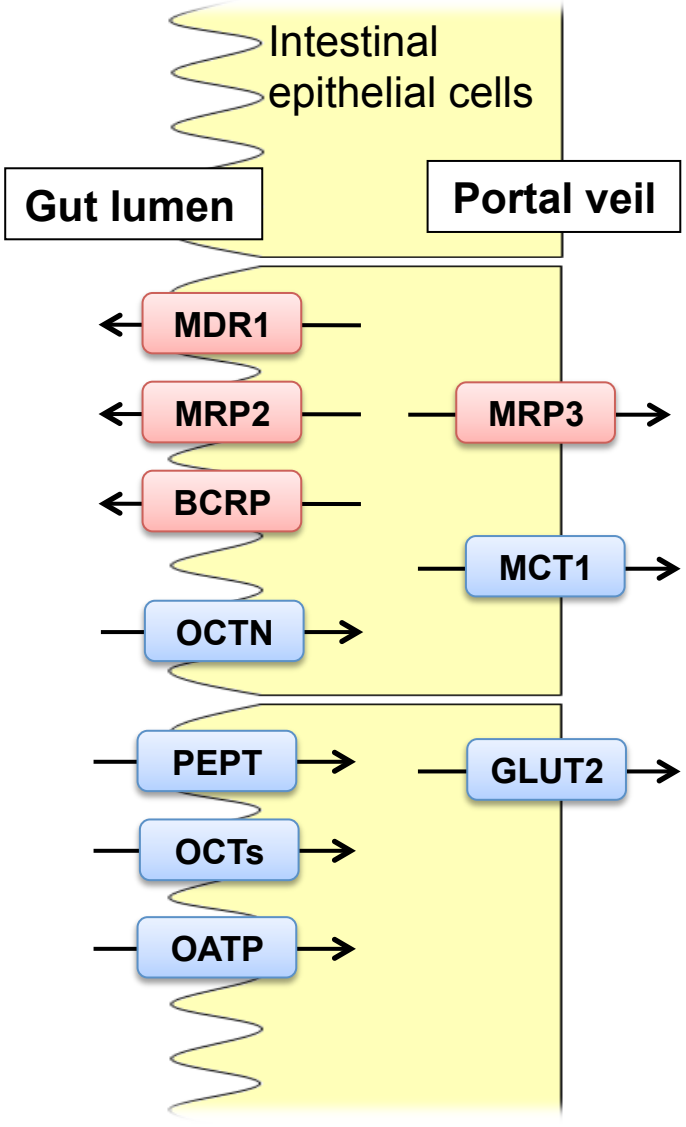
Min et al., *Pharmacotherapy* 13, 1997

Circadian regulation of intestinal expression of ABC transporter



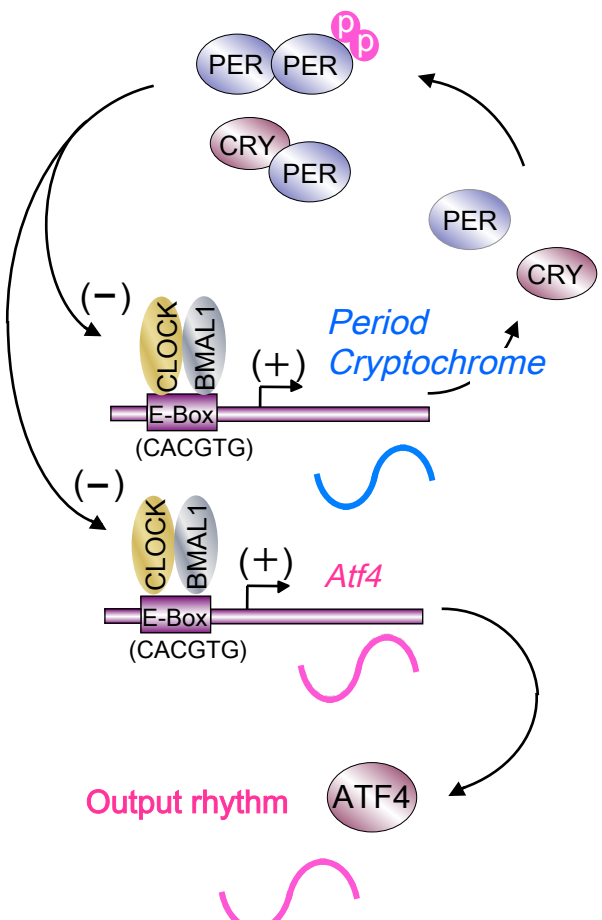
Murakami et al., *Gastroenterology* 2008

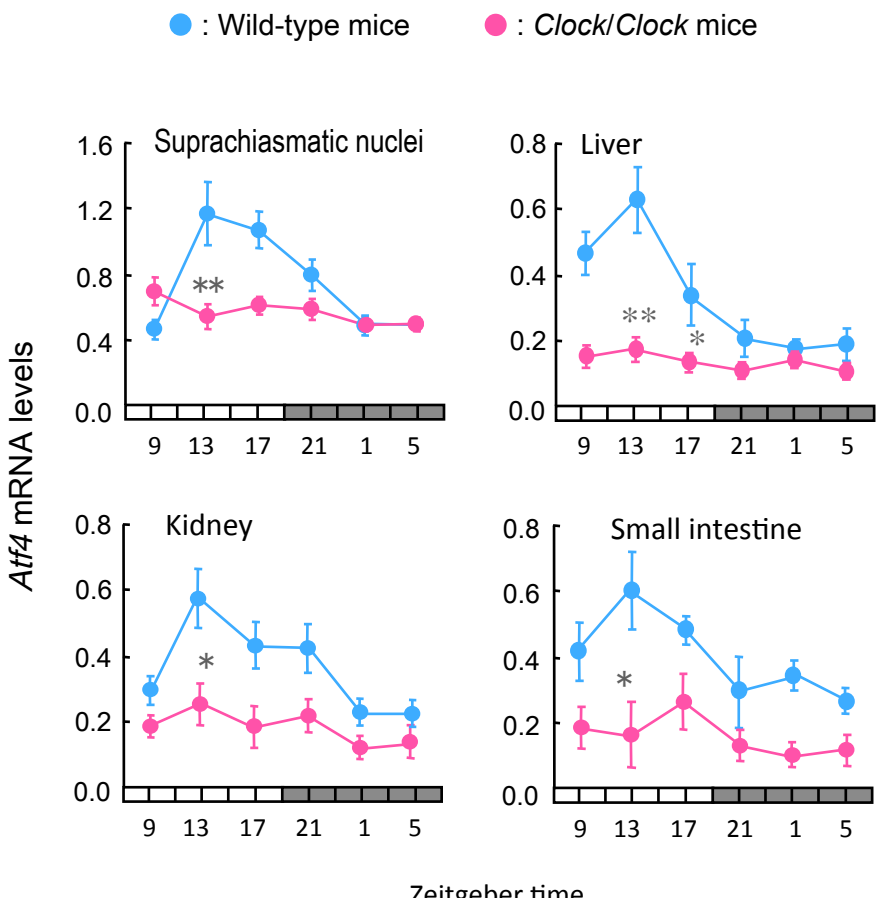
Temporal expression profiles of Abc and Slc transporter genes in small intestine of mice



Pharmacokinetic-related genes		
ABC transporters	SLC transporters	
Abcb1a	*Slc10a1*	*Slco4c1*
Abcb1b	*Slc10a2*	*Slc15a1*
Abcb4	*Slc16a1*	*Slc22a1*
Abcb11	*Slc17a1*	*Slc22a2*
Abcc1	*Slco1a1*	*Slc22a3*
Abcc2	*Slco1a4*	*Slc22a4*
Abcc3	*Slco1a5*	*Slc22a5*
Abcg2	*Slco1a6*	*Slc22a6*
	Slco1b2	*Slc22a7*
	Slco1c1	*Slc22a8*
	Slco2b1	*Slc22a21*
	Slco4a1	

The expression of ATF4 is under the control of circadian clock

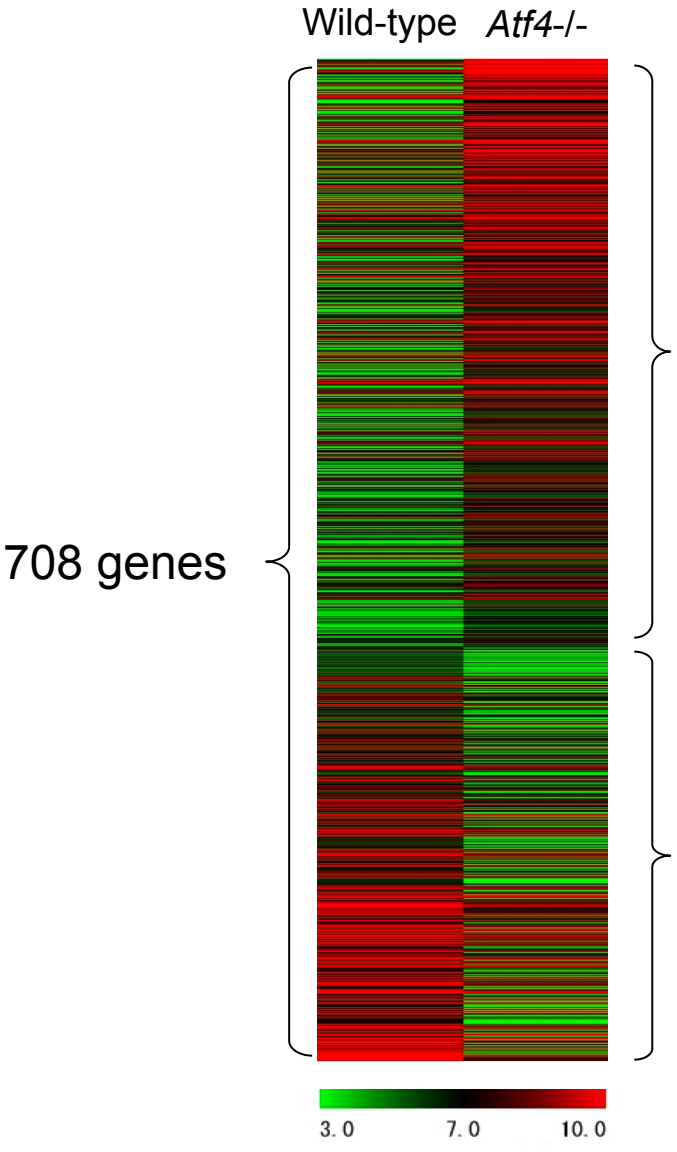




N=4-6,means ± SEM
**P <0.01, *P < 0.05 compared with wild-type group

Koyanagi et al., *J. Biol. Chem.* 2011

Expression of genes under the transcriptional control of ATF4



Up-regulation in *Atf4*-/- cells

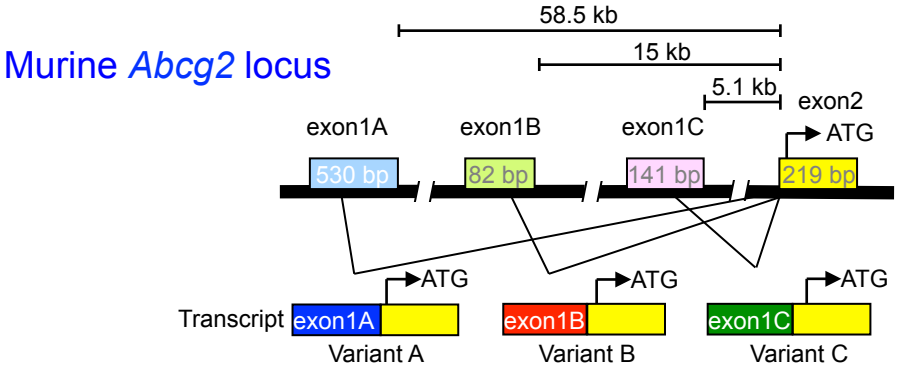
····· 445 genes

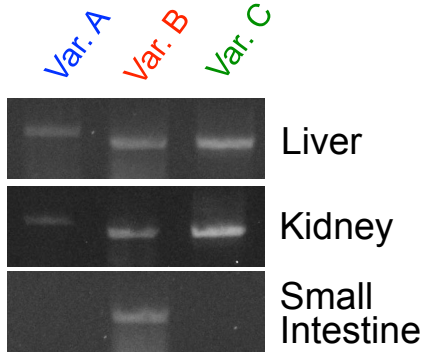
Down-regulation in *Atf4*-/- cells

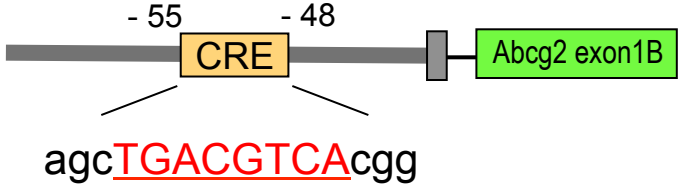
····· 263 genes

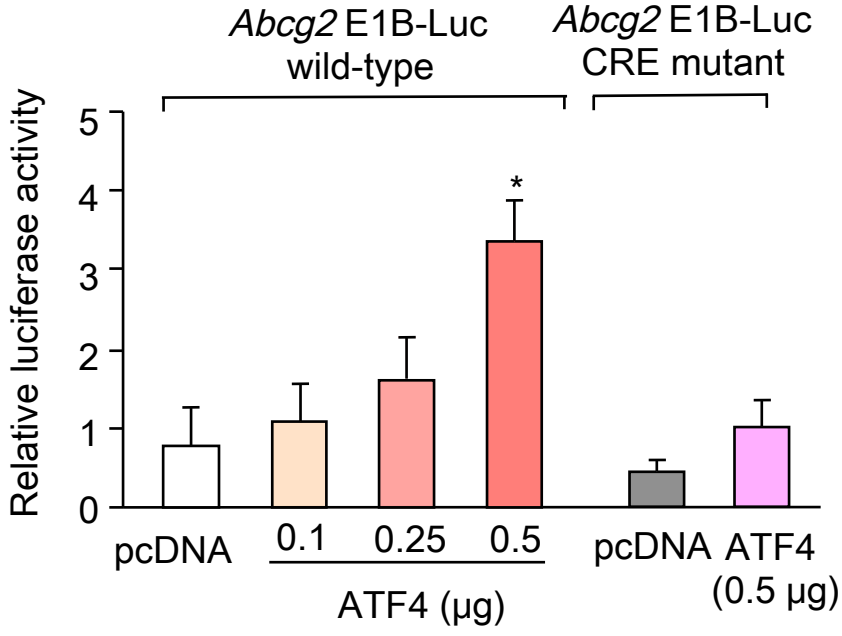
Koyanagi et al., *J. Biol. Chem.* 2011

Circadian regulation of mouse *Abcg2* gene by ATF4



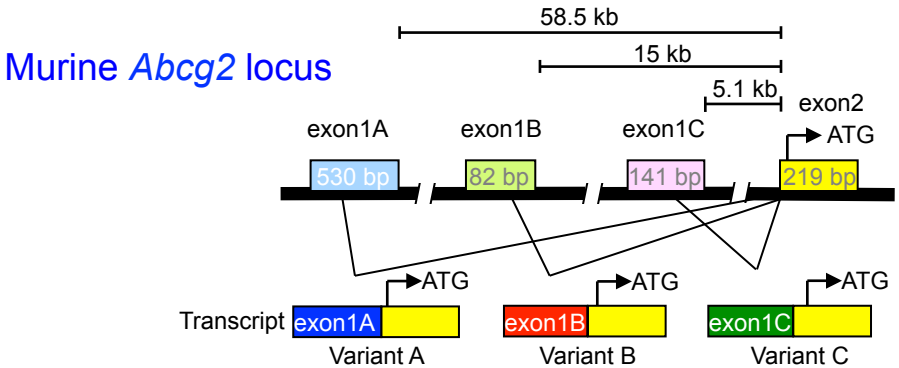


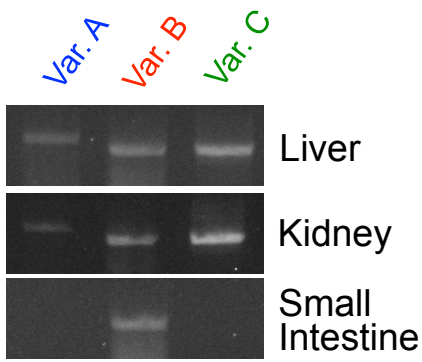


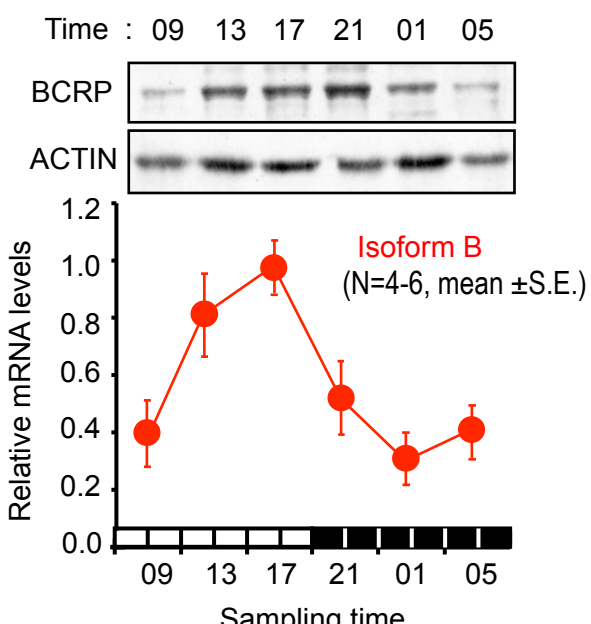


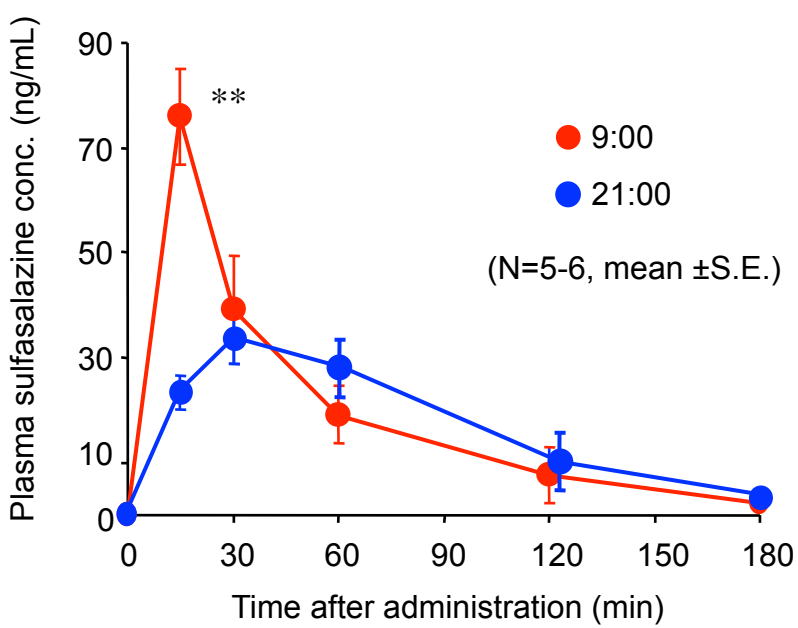
Hamdan et al., *J. Biol. Chem.* 2012

Circadian regulation of mouse *Abcg2* gene by ATF4



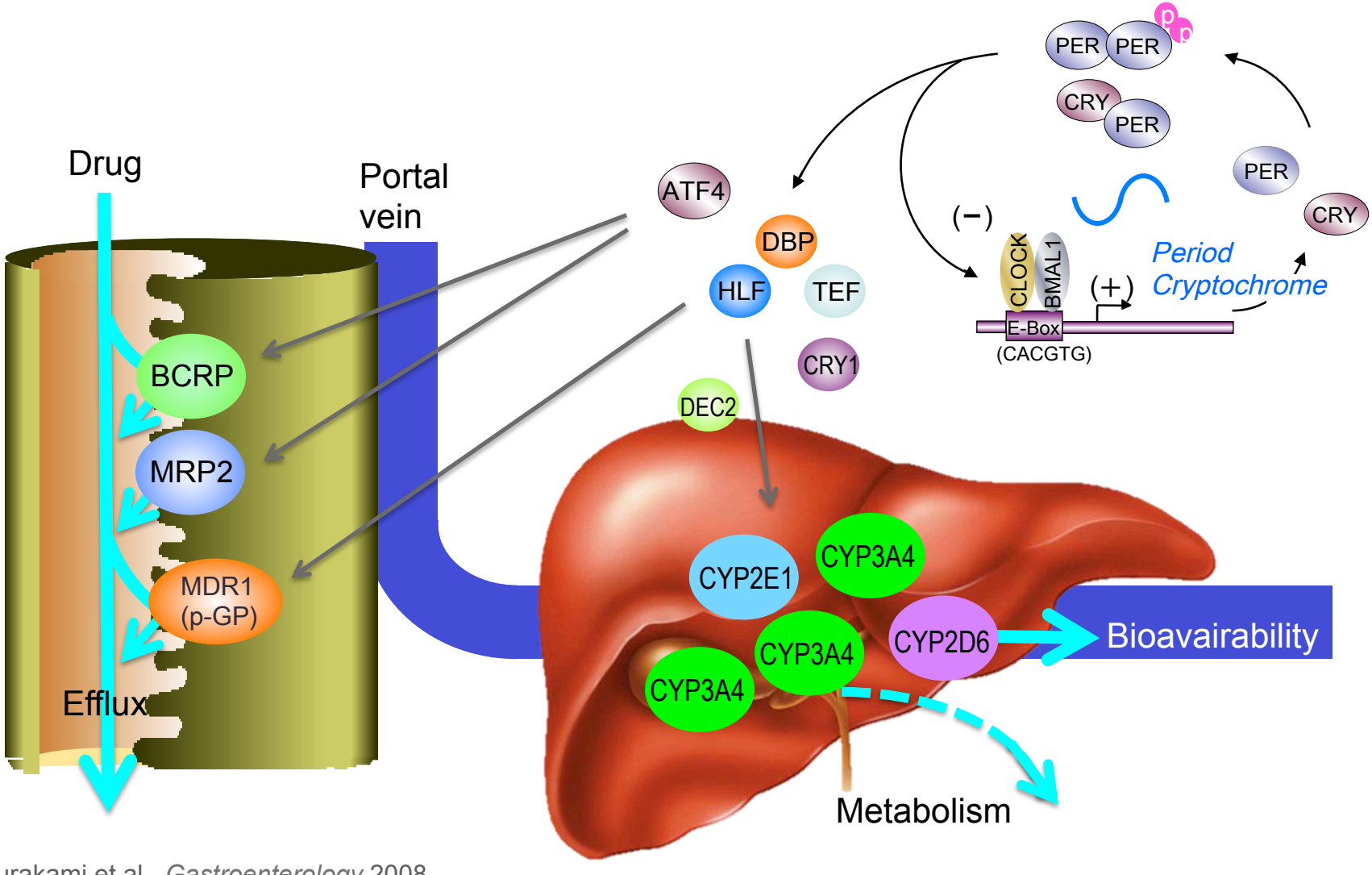






Hamdan et al., *J. Biol. Chem.* 2012

Role of circadian clock in the xenobiotic detoxification system



Murakami et al., *Gastroenterology* 2008
Koyanagi et al., *J. Biol. Chem.* 2011
Hamdan et al., *J. Biol. Chem.* 2012

Takiguchi et al., *Pharmacogenet Genome*, 2007
Matsunaga et al., *Hepatology* 2008
Matsunaga et al., *Mol Pharmacol* 2012

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