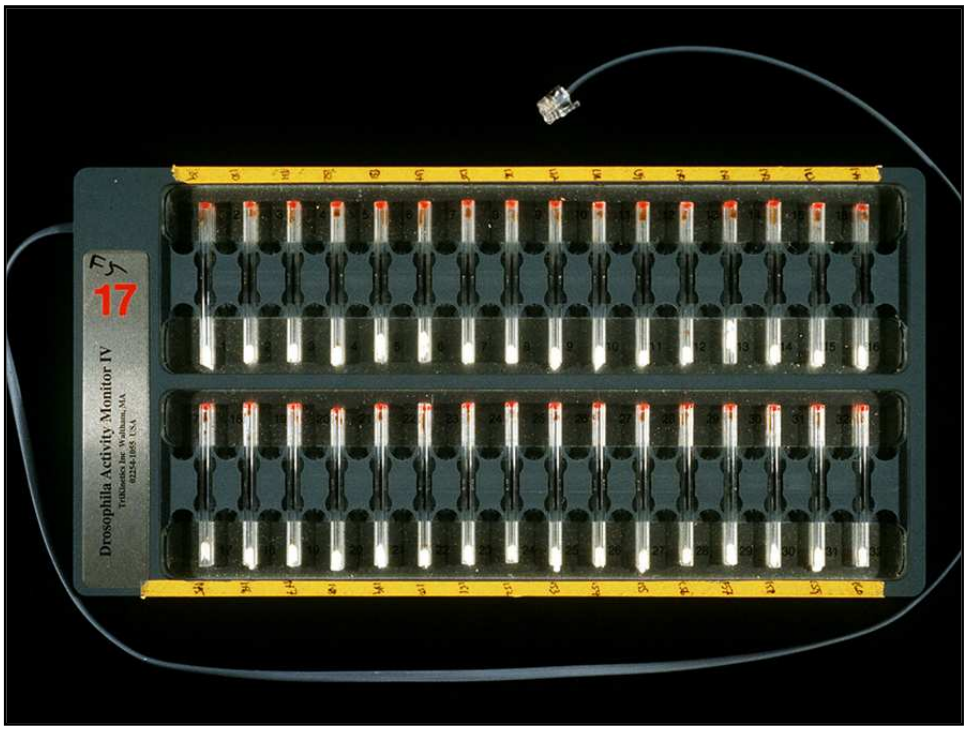
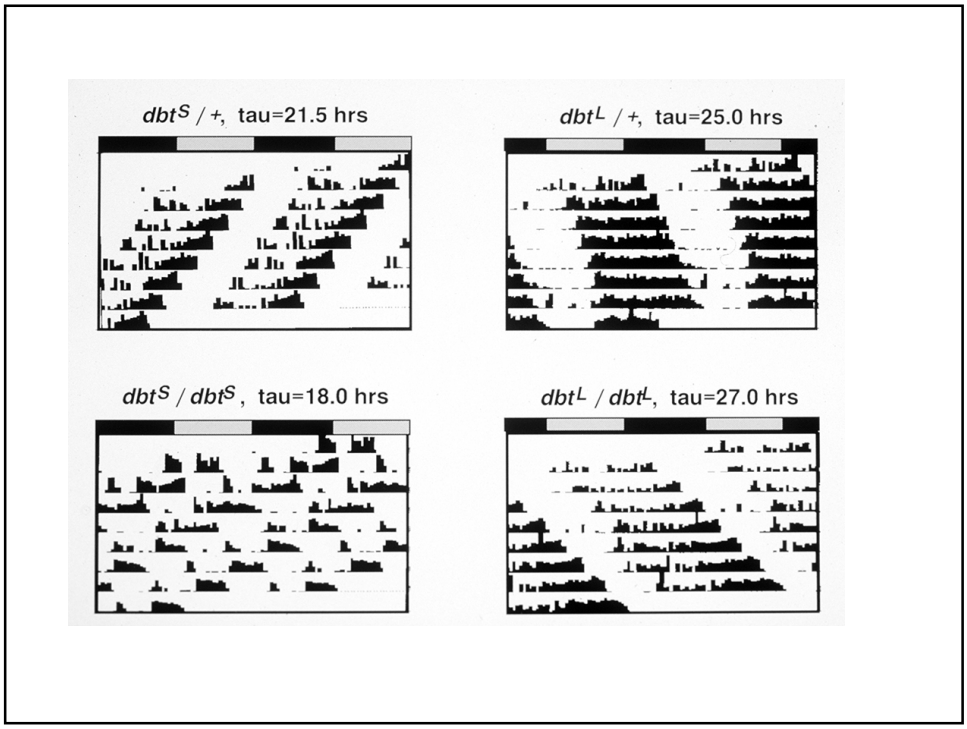
This Week in *Science*

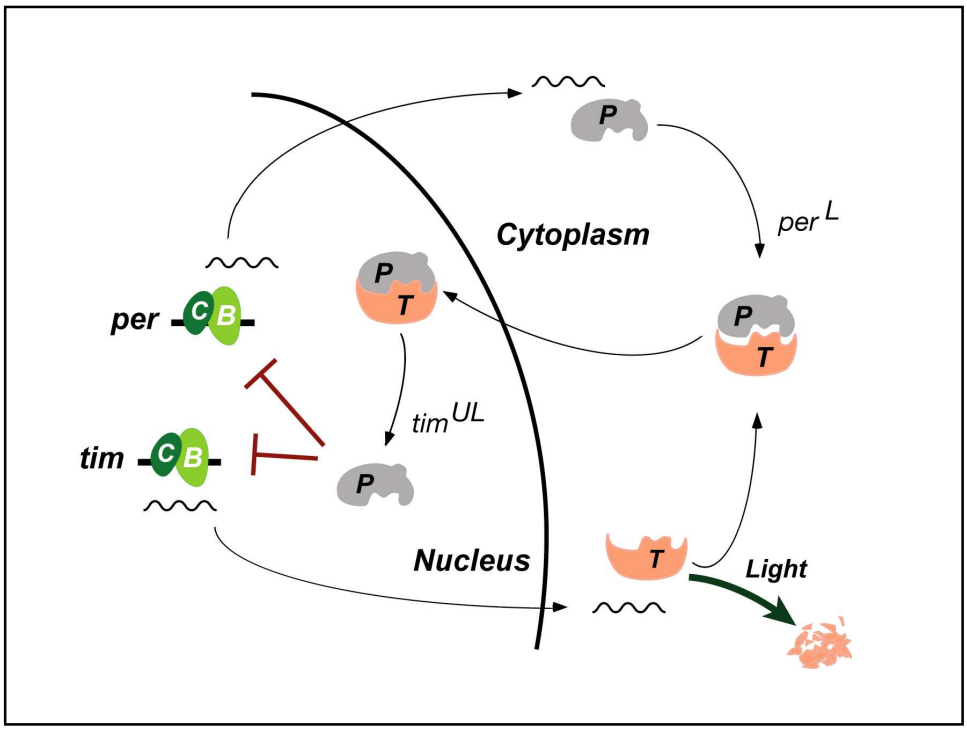
A Family of Larks

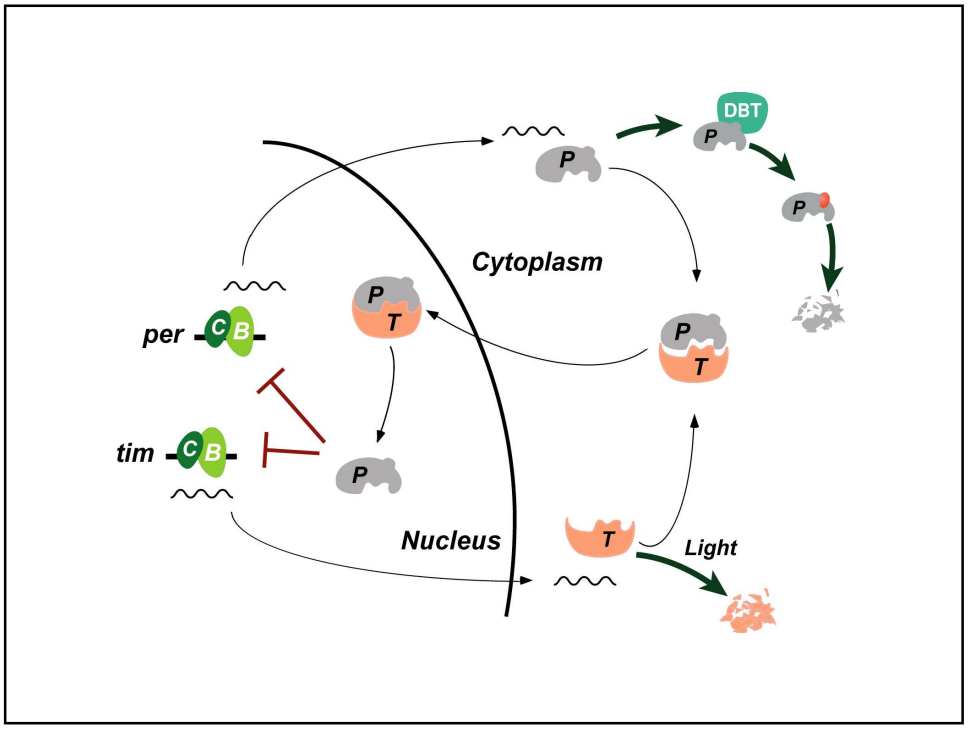
Familial advanced sleep phase syndrome is inherited autosomally. These individuals have unusual sleep cycles and wake up abnormally early each morning. In one such family this characteristic is due to a single nucleotide mutation in the human Period2 gene; this blocks phosphorylation by casein kinase Iε. In a satisfying parallel with studies in animals, a deficit in such phosphorylation shortens the animal's circadian period, due to altered function of per in the molecular feedback loops that make up the circadian clock. This striking effect of a genetic polymorphism on human behavior paves the way to understanding the basis of human variation in daily rhythms.

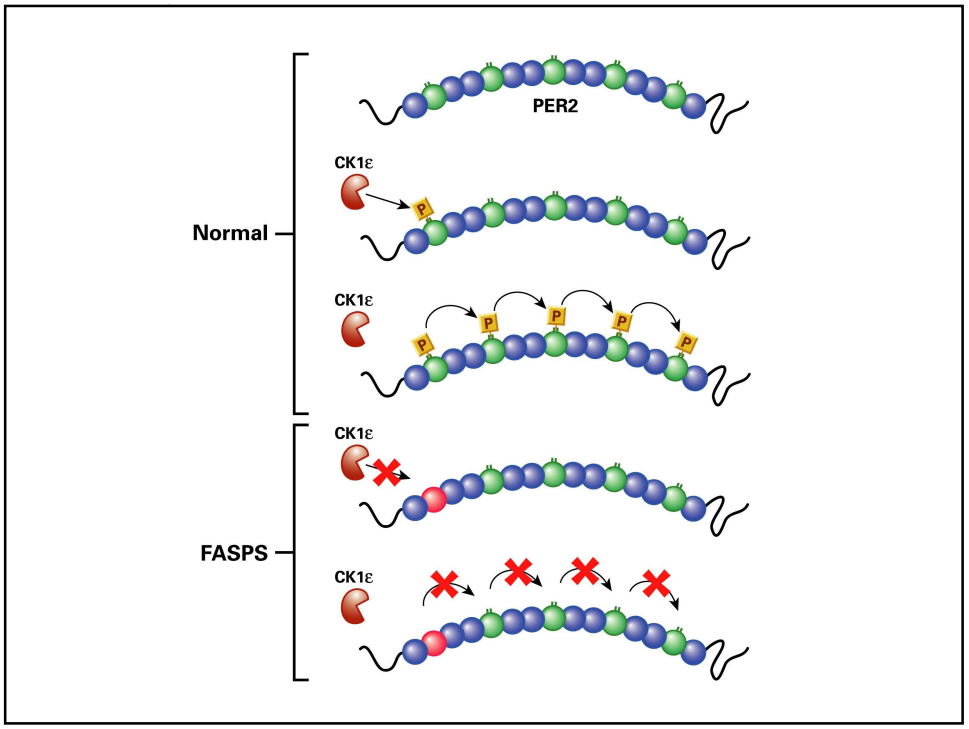
02/09/01

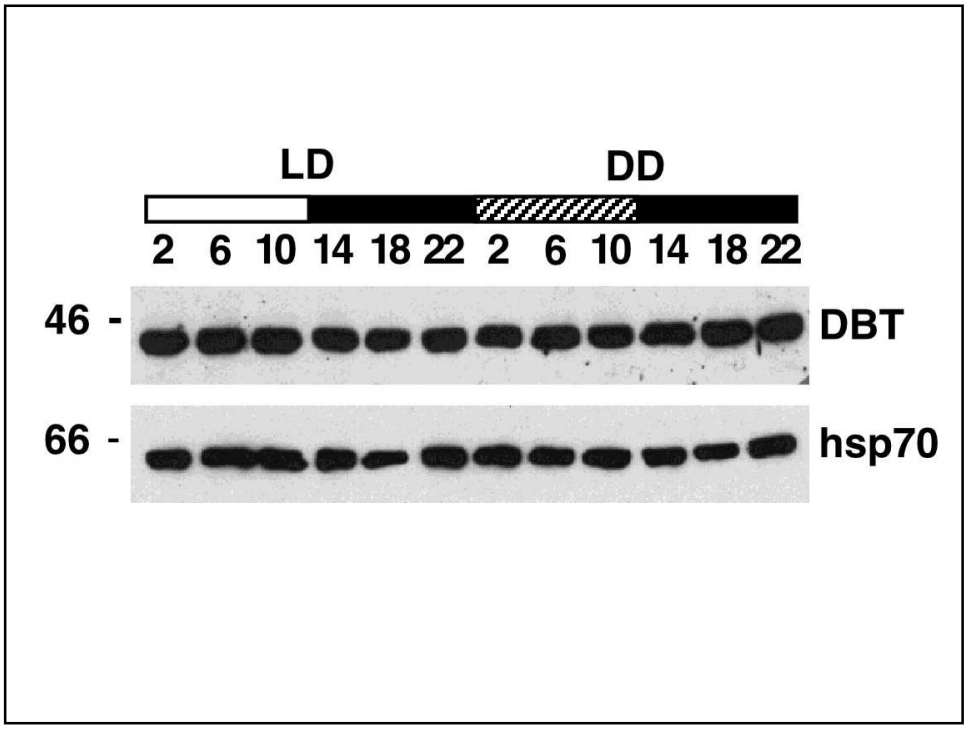


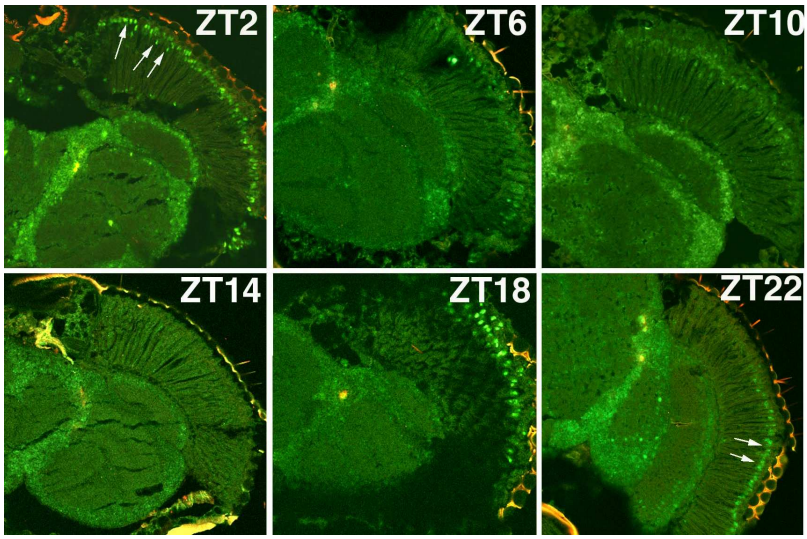

dbt^S / +, tau=21.5 hrs
dbt^L / +, tau=25.0 hrs
dbt^S / dbt^S, tau=18.0 hrs
dbt^L / dbt^L, tau=27.0 hrs

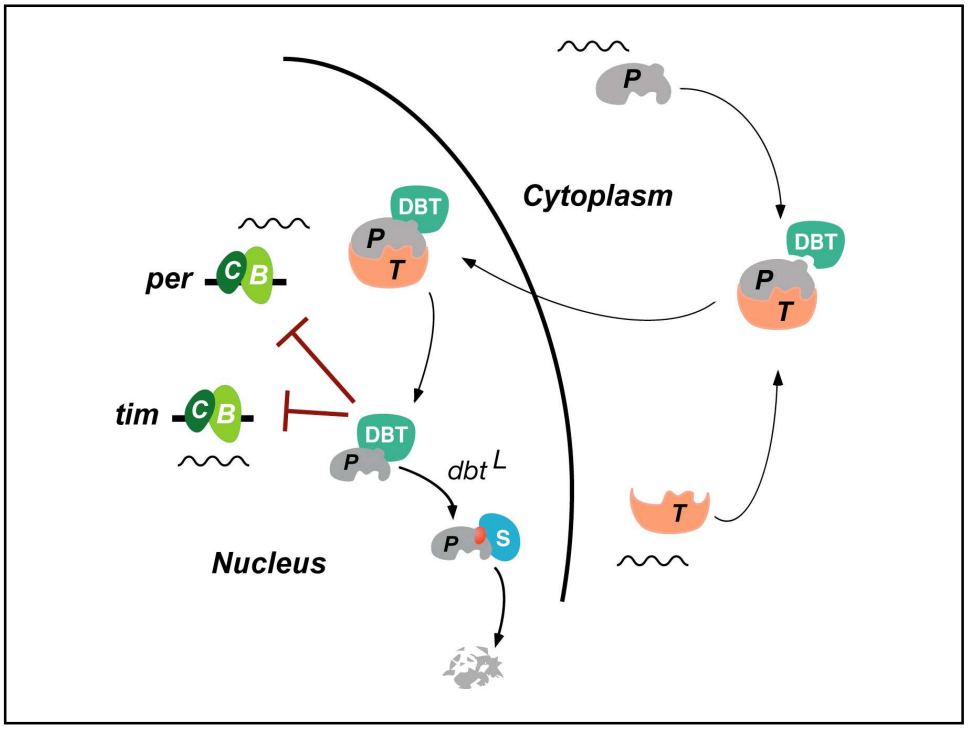

P
Cytoplasm
per^L
per
C
B
P
T
P
T
tim^UL
tim
C
B
P
Nucleus
T
Light

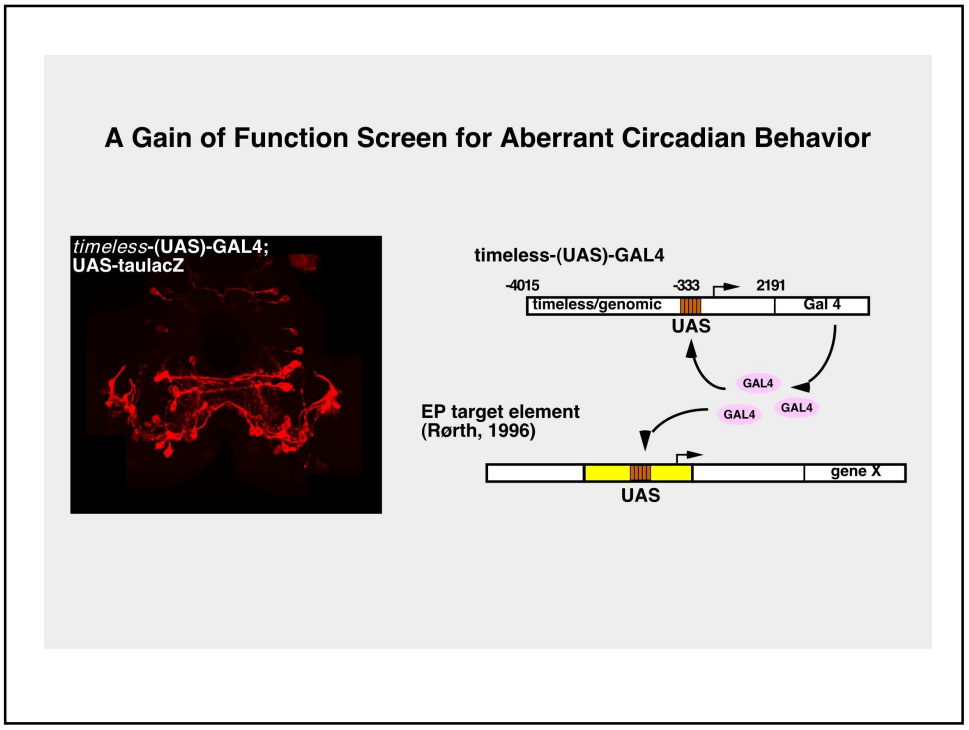

DBT
P
P
P
Cytoplasm
per
C
B
P
T
P
T
tim
C
B
P
Nucleus
T
Light

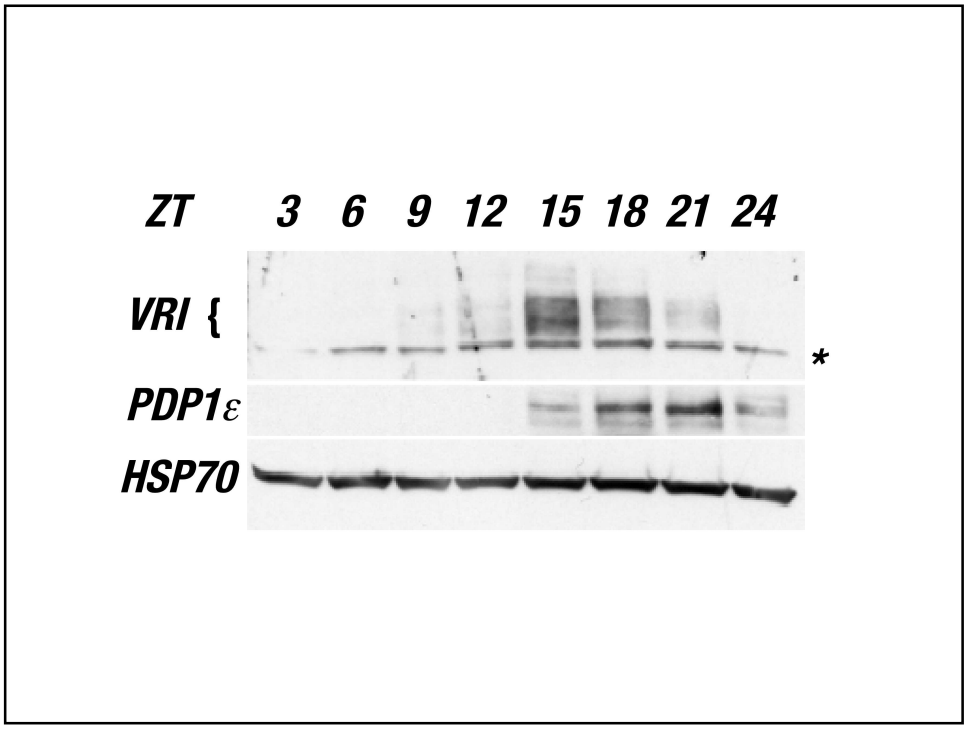

PER2
CK1ε
Normal
P
CK1ε
P
P
P
P
P
CK1ε
FASPS
CK1ε

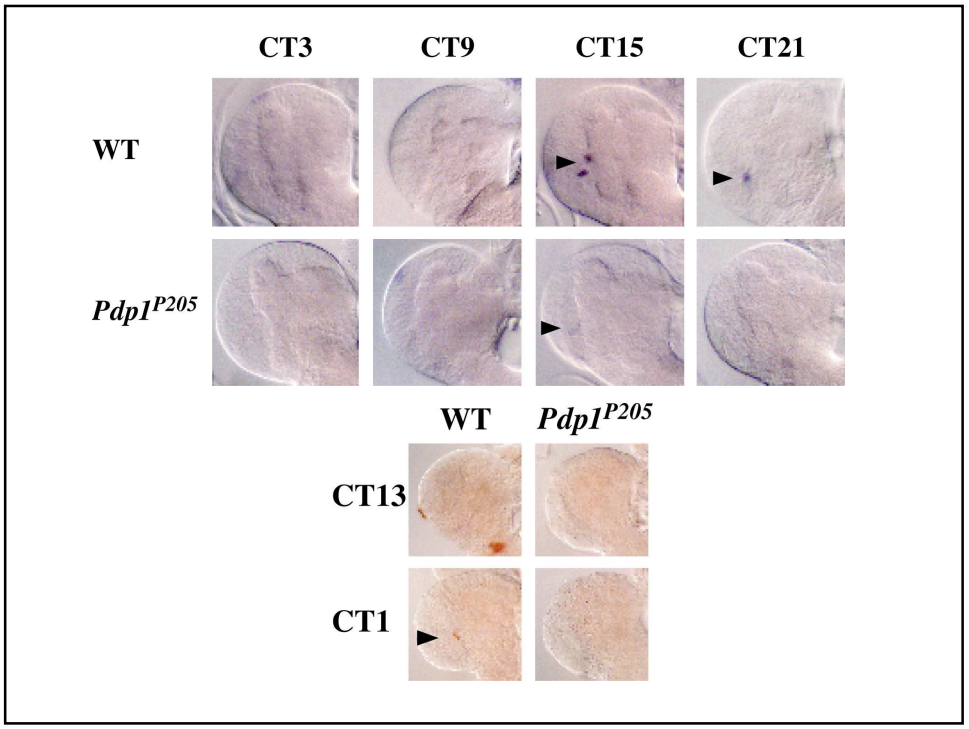

LD
DD
2 6 10 14 18 22 2 6 10 14 18 22
46 -
DBT
66 -
hsp70

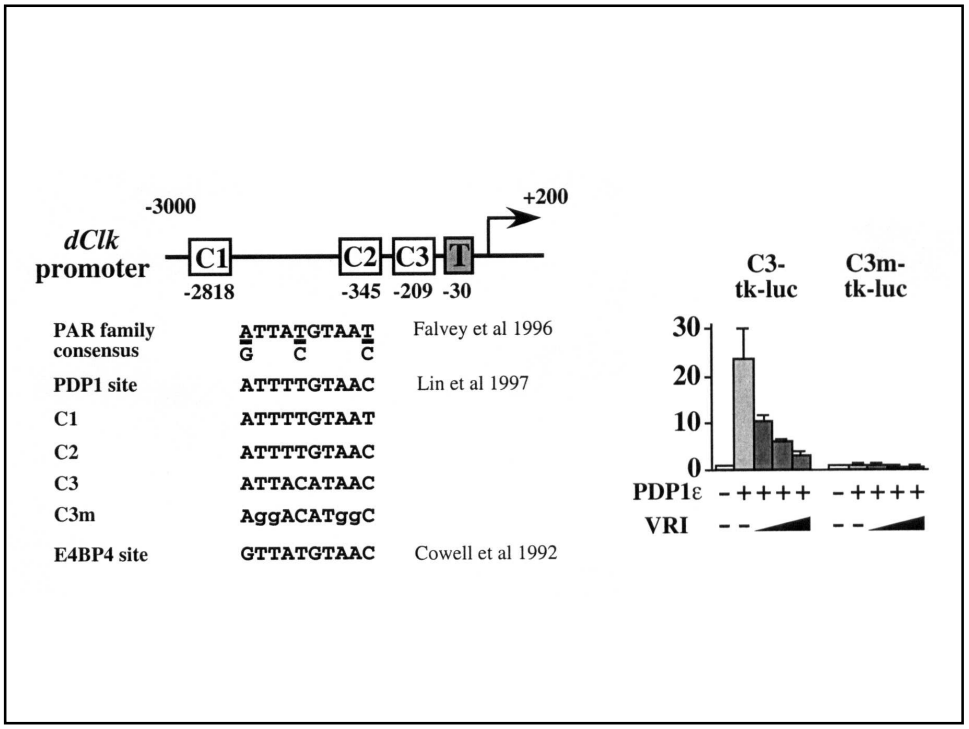

ZT2
ZT6
ZT10
ZT14
ZT18
ZT22

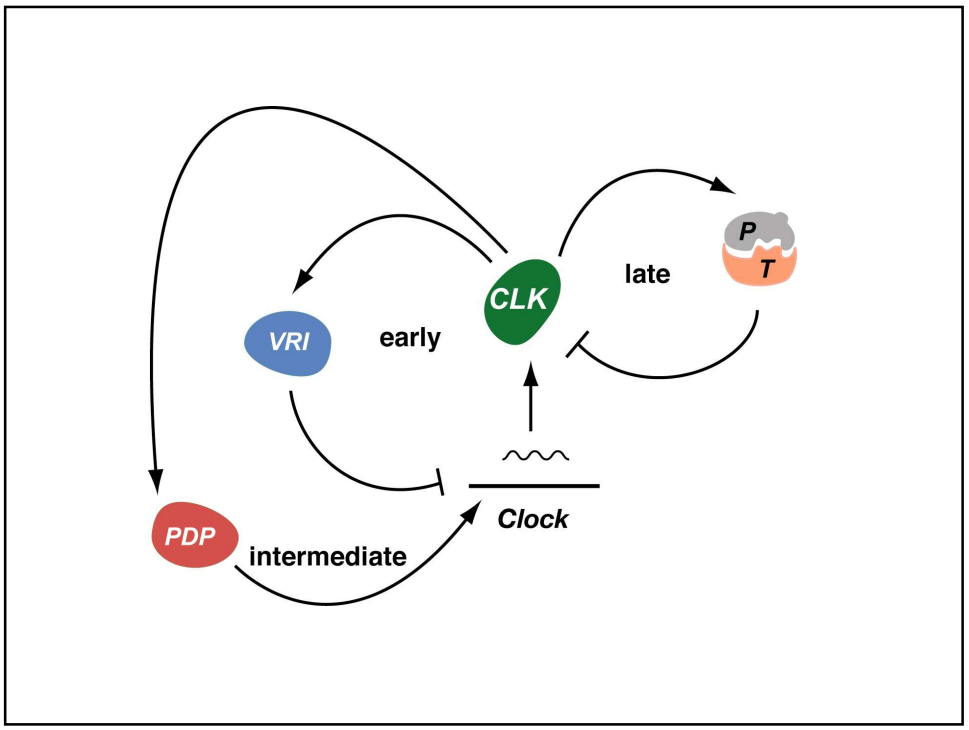

P
Cytoplasm
DBT
P
T
per
C
B
DBT
P
T
tim
C
B
DBT
P
dbt L
T
P
S
Nucleus

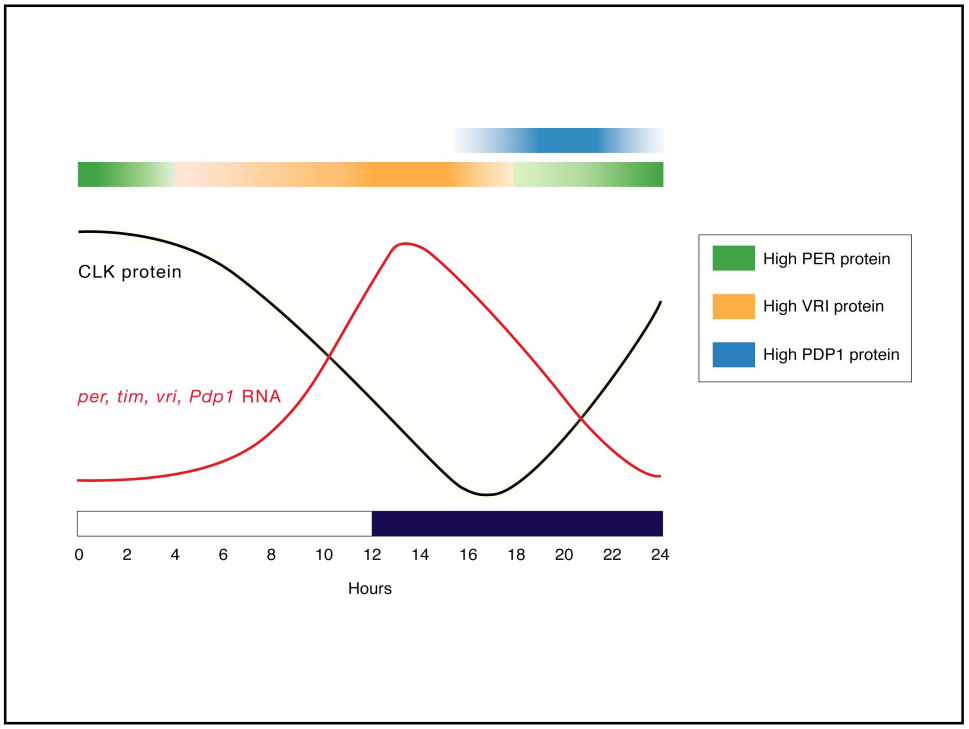

A Gain of Function Screen for Aberrant Circadian Behavior
timeless-(UAS)-GAL4;
UAS-taulacZ
timeless-(UAS)-GAL4
-4015
-333
2191
timeless/genomic
Gal 4
UAS
GAL4
GAL4
GAL4
EP target element
(Rørth, 1996)
gene X
UAS

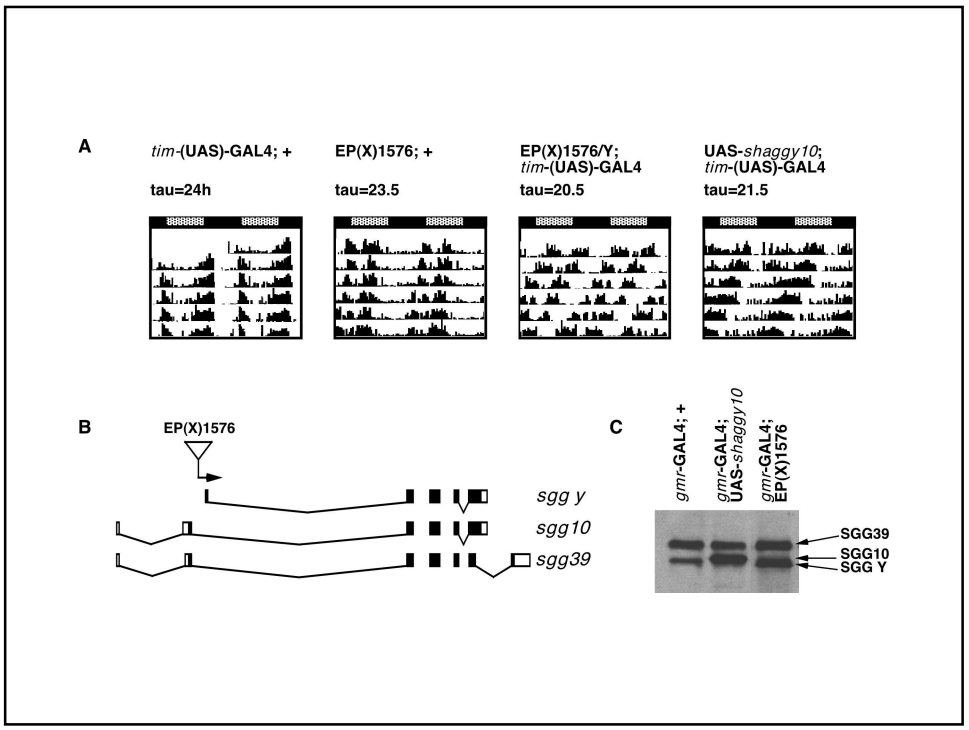

ZT 3 6 9 12 15 18 21 24
VRI
PDP1ε
HSP70
*

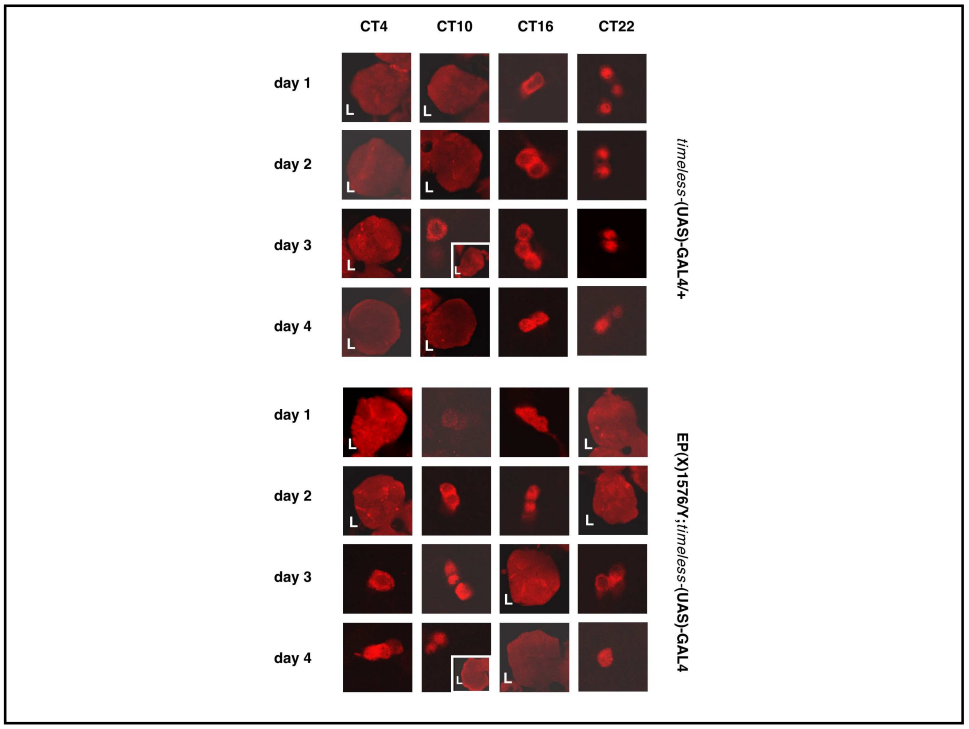

CT3
CT9
CT15
CT21
WT
Pdp1P205
WT
Pdp1P205
CT13
CT1

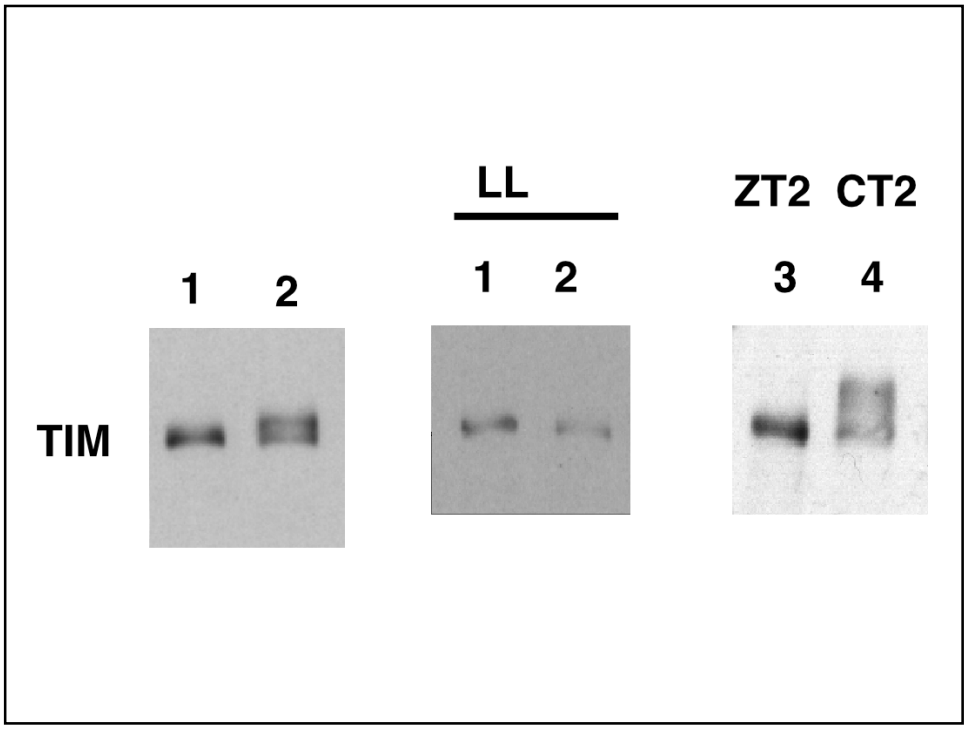

-3000
+200
dClk promoter
C1
C2
C3
T
-2818
-345
-209
-30
PAR family consensus
ATTATGTAAT
G C C
PDP1 site
ATTTTGTAAC
Lin et al 1997
C1
ATTTTGTAAT
C2
ATTTTGTAAC
C3
ATTACATAAC
C3m
AggACATggC
E4BP4 site
GTTATGTAAC
Cowell et al 1992
Falvey et al 1996
C3-tk-luc
C3m-tk-luc
30
20
10
0
PDP1ε - + + + + - + + + +
VRI - - - -

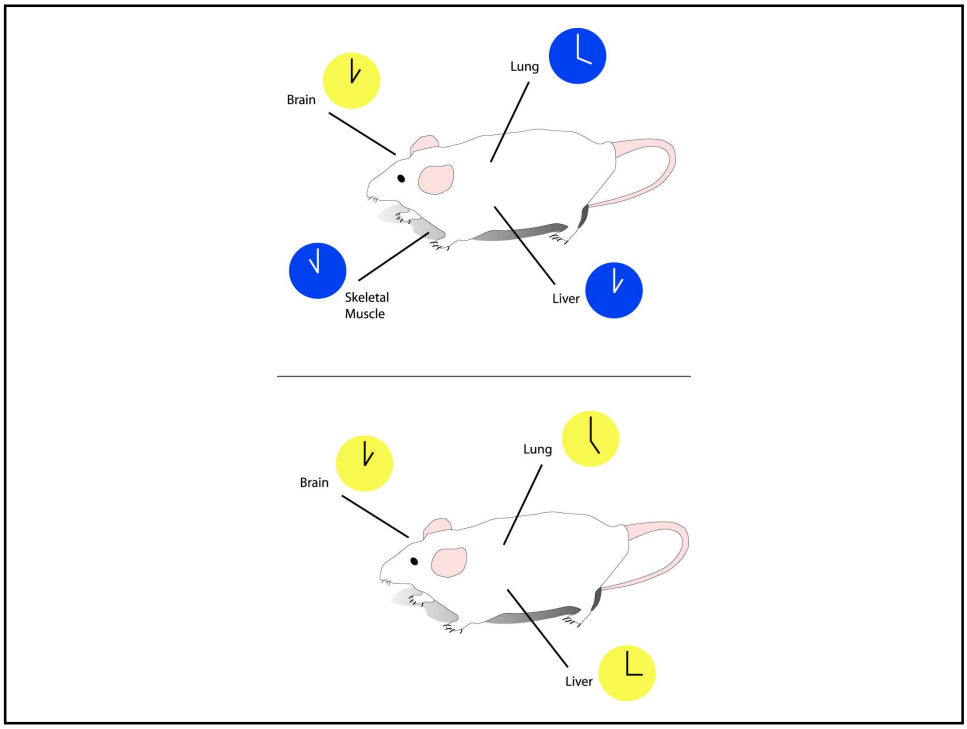

CLK
P
T
late
VRI
early
Clock
PDP
intermediate

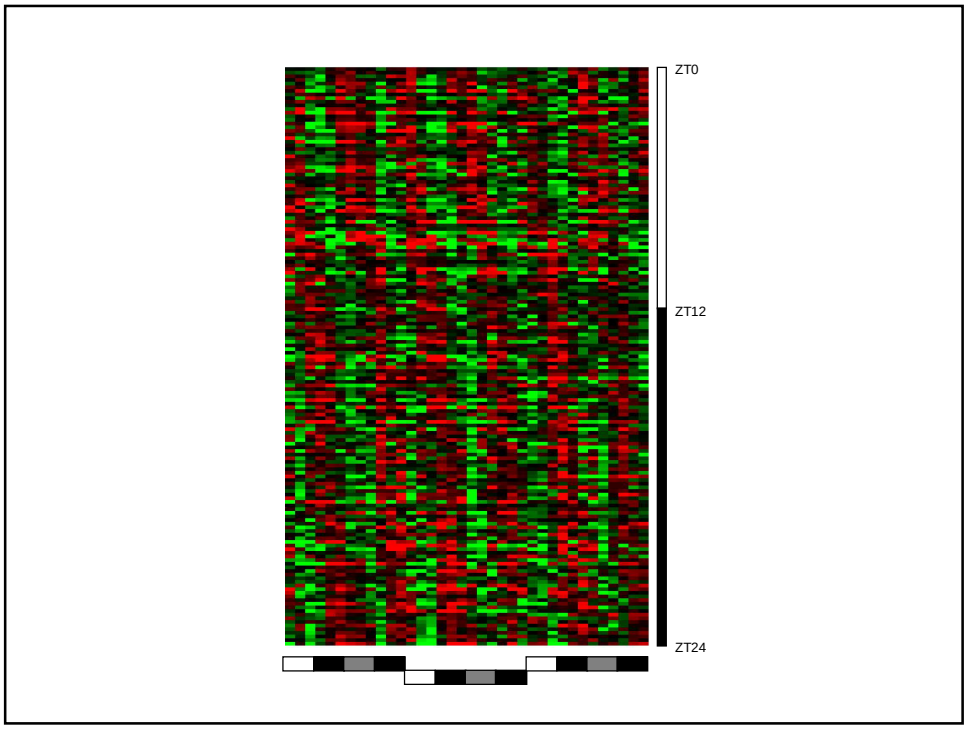

CLK protein
per, tim, vri, Pdp1 RNA
High PER protein
High VRI protein
High PDP1 protein
0 2 4 6 8 10 12 14 16 18 20 22 24
Hours

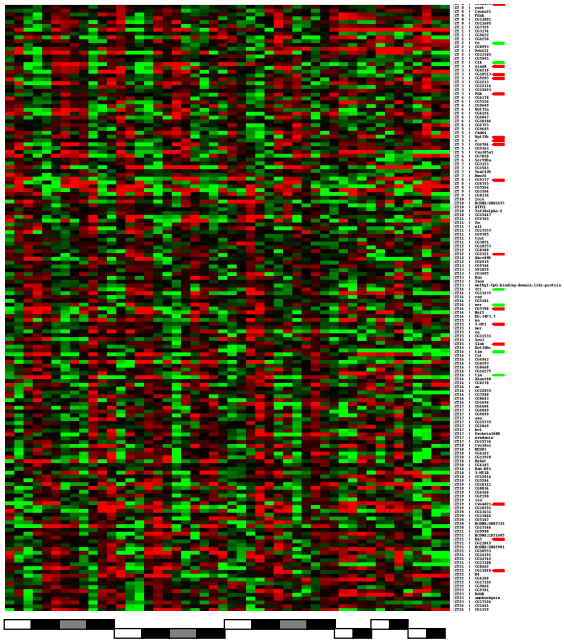

A
tim-(UAS)-GAL4; +
tau=24h
EP(X)1576; +
tau=23.5
EP(X)1576/Y;
tim-(UAS)-GAL4
tau=20.5
UAS-shaggy10;
tim-(UAS)-GAL4
tau=21.5
B
EP(X)1576
sgg y
sgg10
sgg39
C
gmr-GAL4; +
gmr-GAL4;
UAS-shaggy10
gmr-GAL4;
EP(X)1576
SGG39
SGG10
SGG Y

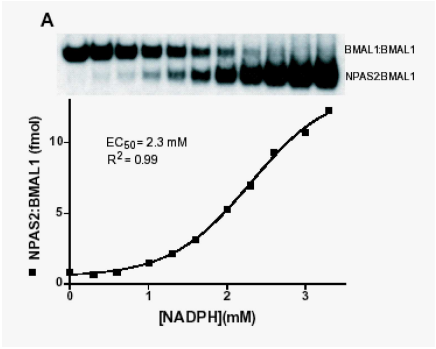

CT4
CT10
CT16
CT22
day 1
day 2
day 3
day 4
timeless-(UAS)-GAL4/+
day 1
day 2
day 3
day 4
EP(X)1576/Y;timeless-(UAS)-GAL4


LL
ZT2 CT2
1 2
1 2
3 4
TIM


Brain
Lung
Skeletal Muscle
Liver
Brain
Lung
Liver


ZT0
ZT12
ZT24





Rutter et al., *Science* **293**, 510 (2001)

Lipid Metabolism	phospholipase A2	CG1583	ZT 7
	ATP-citrate (pro-S)-lyase	ATPCL	ZT10
	alkylglycerone-phosphate synthase	CG10253	ZT12
	myo-inositol-1-phosphate synthase	Inos	ZT13
	long-chain-fatty-acid-CoA-ligase	BcDNA:GH02901	ZT21
Carbohydrate Metabolism	fructose-bisphosphatase	CG10611	ZT 0
	glucose-6-phosphate 1-dehydrogenase	Zw	ZT11
	heparan sulfate 6-O-sulfotransferase	Hs6st	ZT18
	glucan 1,4-alpha-glucosidase	BcDNA:GH02712	ZT20
	beta glucosidase like	CG9701	ZT23
Glycoprotein biosynthesis	mannosyl transferase	CG12311	ZT14
	mannosyltransferase-like	EG:34F3.7	ZT14
Oxidoreductases	oxidoreductase	Pdh	ZT 3
	3-hydroxyisobutyrate dehydrogenase	CG15093	ZT 3
	sepiapterin reductase	CG12116	ZT 3