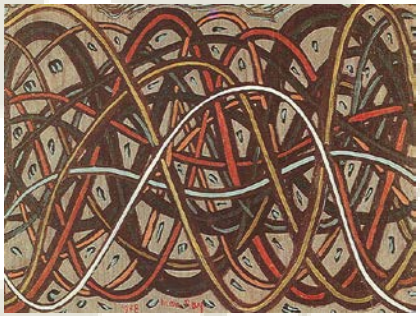
Toward Systems Cancer Chronotherapeutics and its integration into home care.

Francis Lévi, MD, PhD



Warwick Medical School

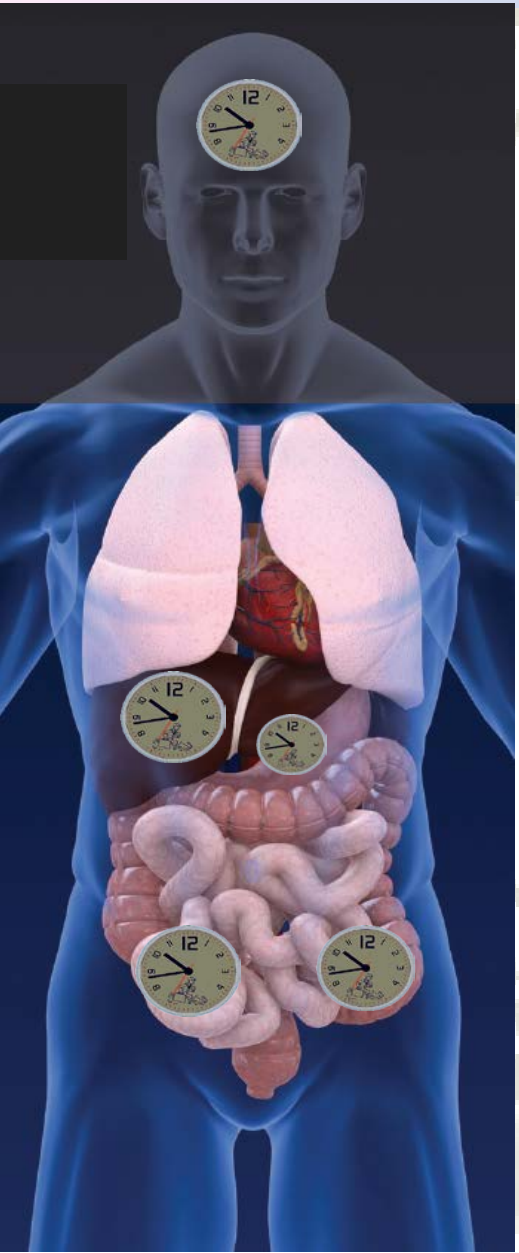
Cancer Chronotherapy Unit
Cancer Research Unit

Rythmes Biologiques et Cancers UMR S776

Paul Brousse hospital, Villejuif (France)

Inserm

Université Paris Sud



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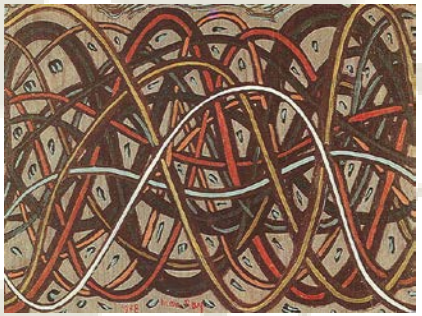

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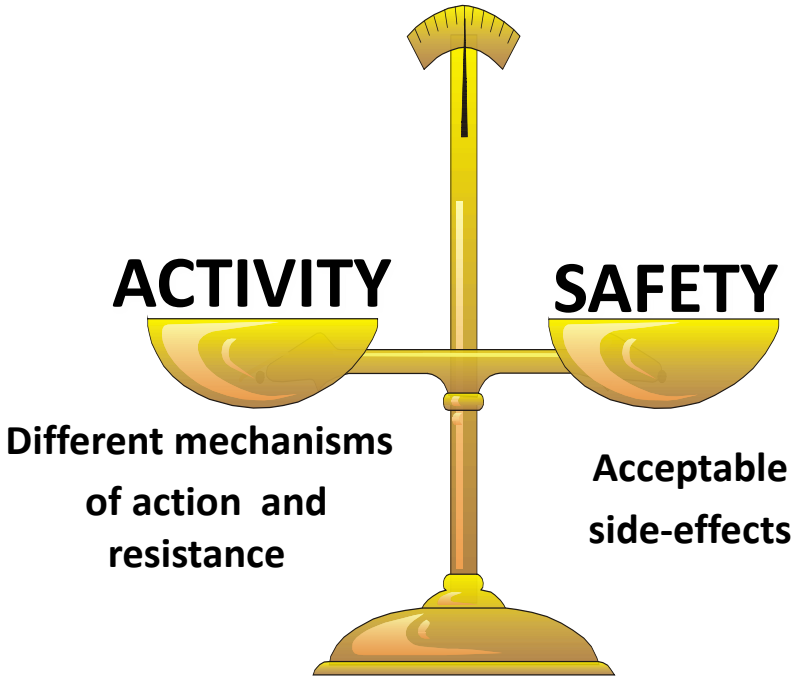
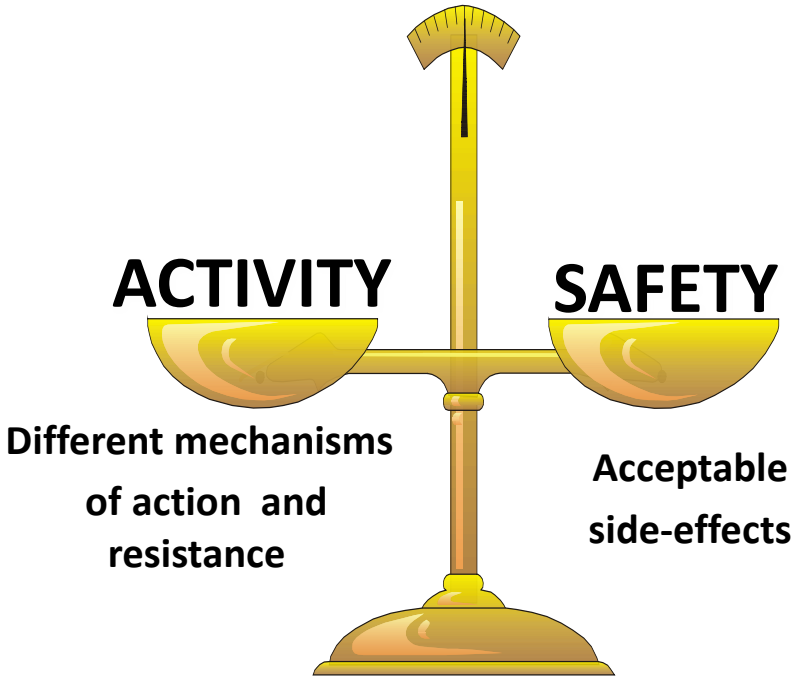
Cancer treatments
finding the right balance between safety and efficacy



- Dose
- Schedule
- Combinations
- Route

Cancer treatments
finding the right balance between safety and efficacy



- Dose
- Schedule
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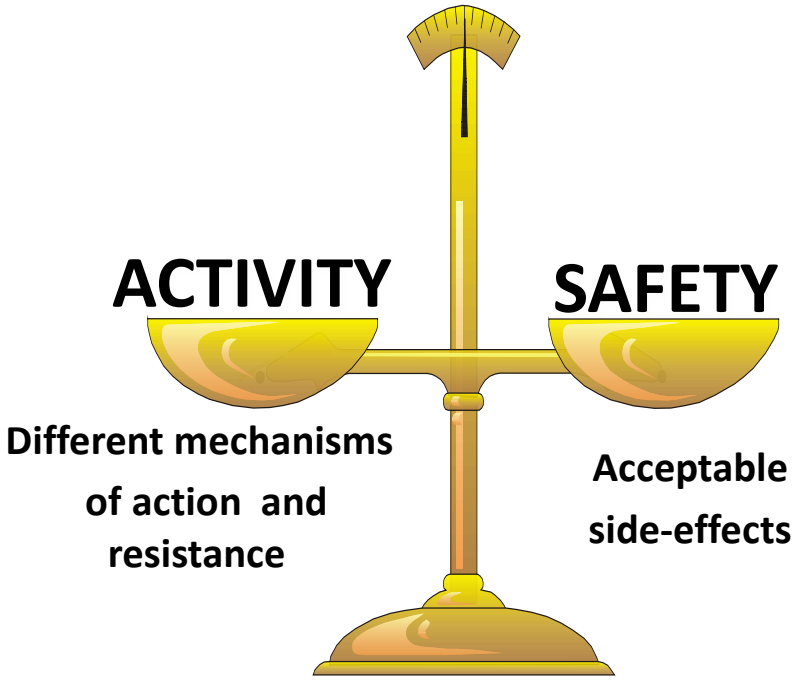
- Route

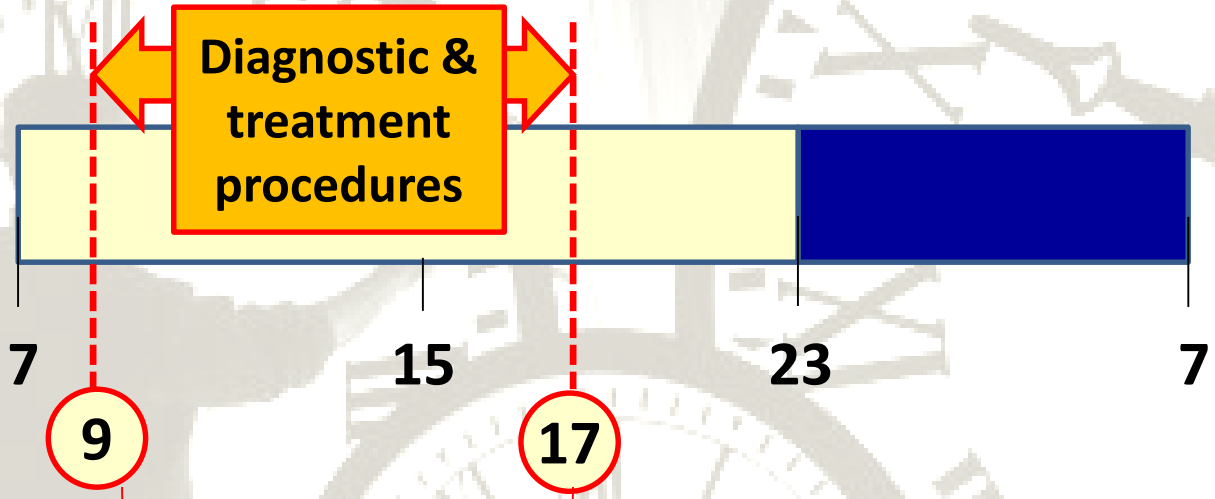
Relevance of biological timing systems?

Cancer treatments
finding the right balance between safety and efficacy



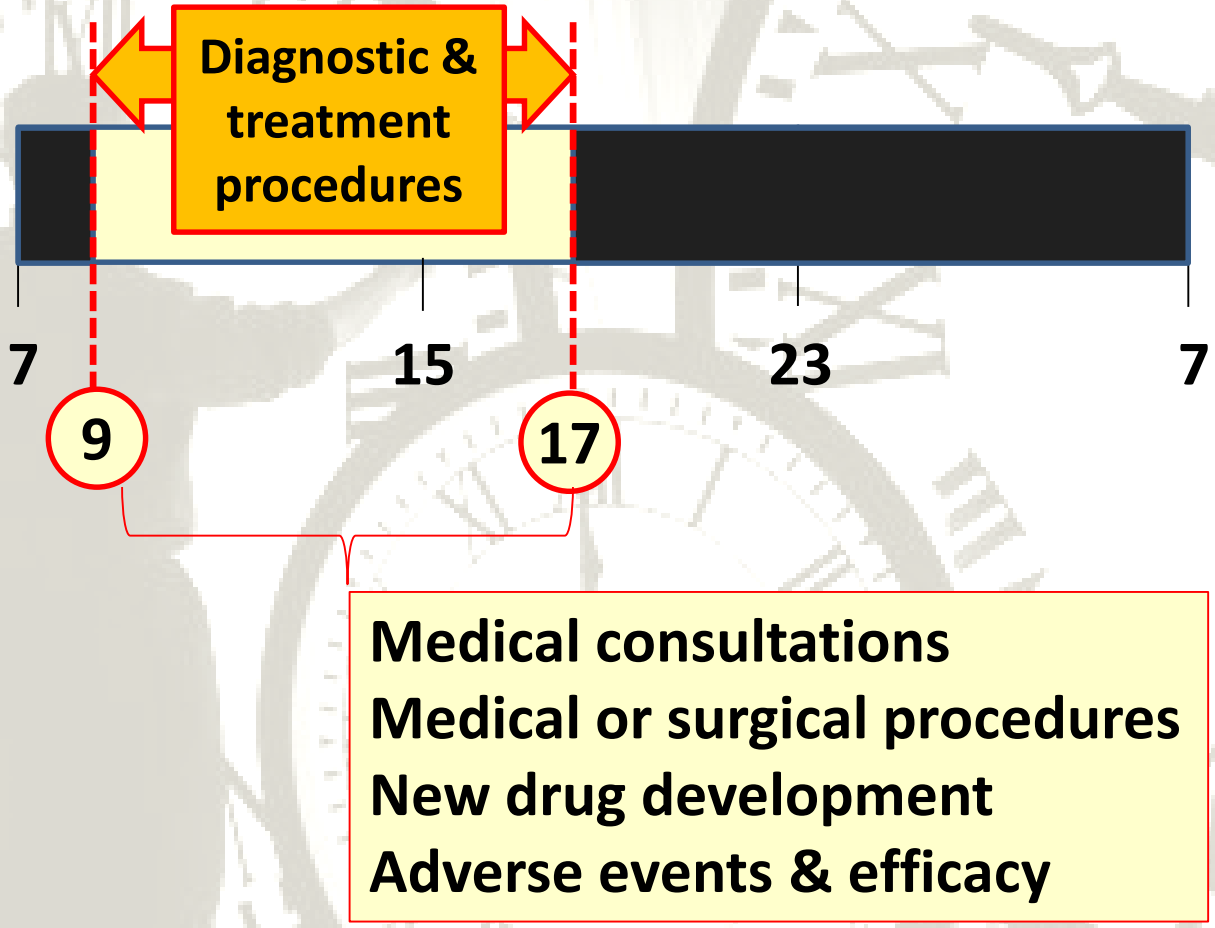
Relevance of biological timing systems?

Usual timing of cancer treatments

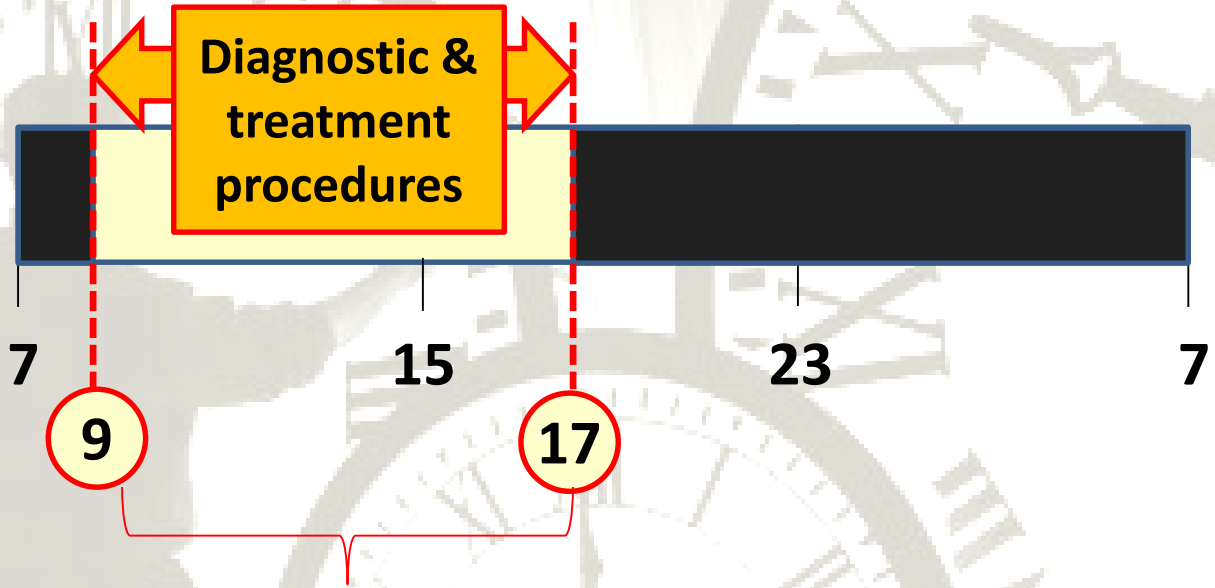


Medical consultations
Medical or surgical procedures
New drug development
Adverse events & efficacy

Usual timing of cancer treatments



Usual timing of cancer treatments



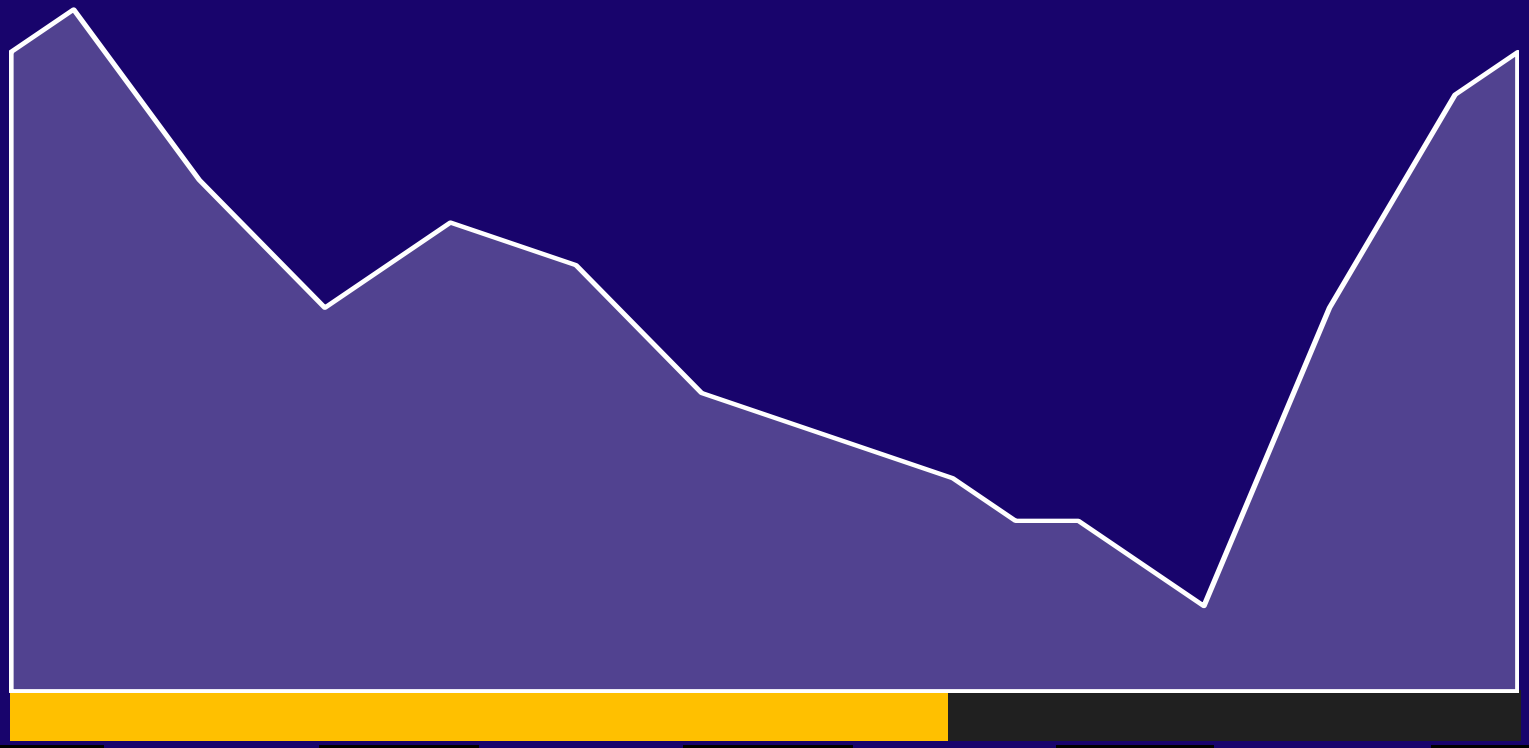
Medical consultations
Medical or surgical procedures
New drug development
Adverse events & efficacy

Hypothesis:
Biological functions operate at constant or random pace

Systems Cancer Chronotherapeutics

Systems Cancer Chronotherapeutics

Serum cortisol (0-16 µg/ml)



08:00 16:00 20:00 04:00 08:00

Clock time (h)

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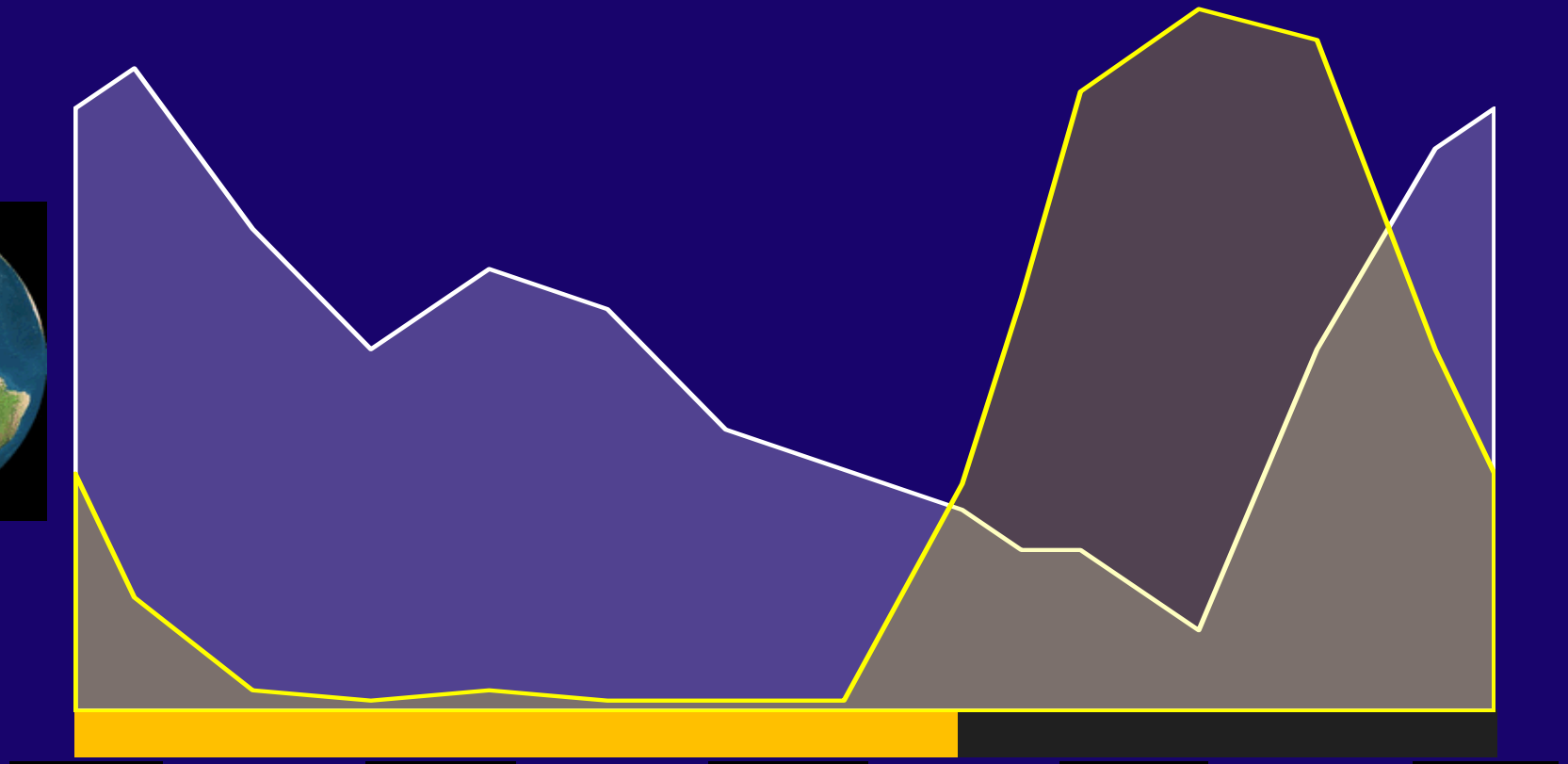
Serum cortisol (0-16 µg/ml)

Serum melatonin (0-70 pg/ml)



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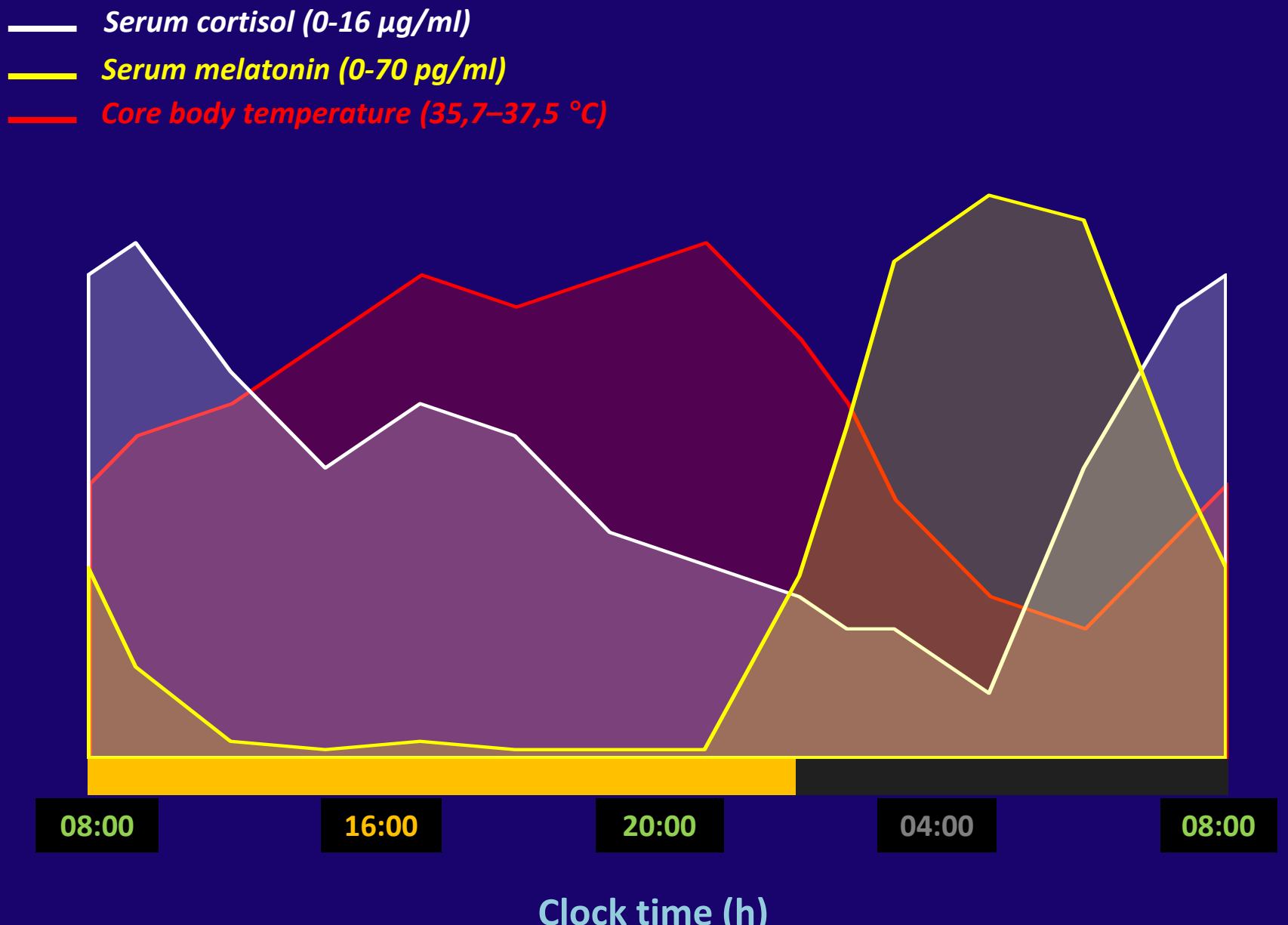
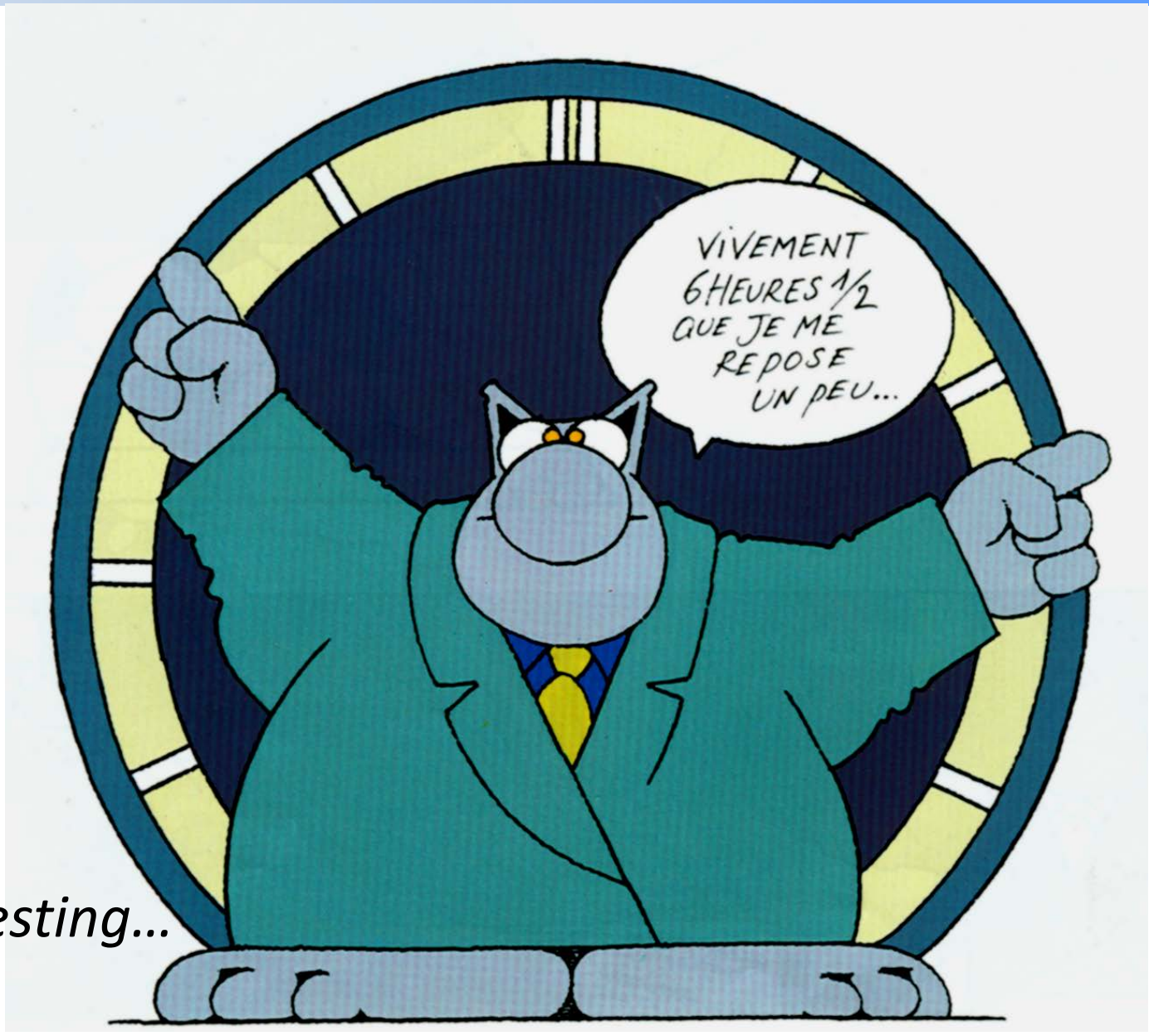
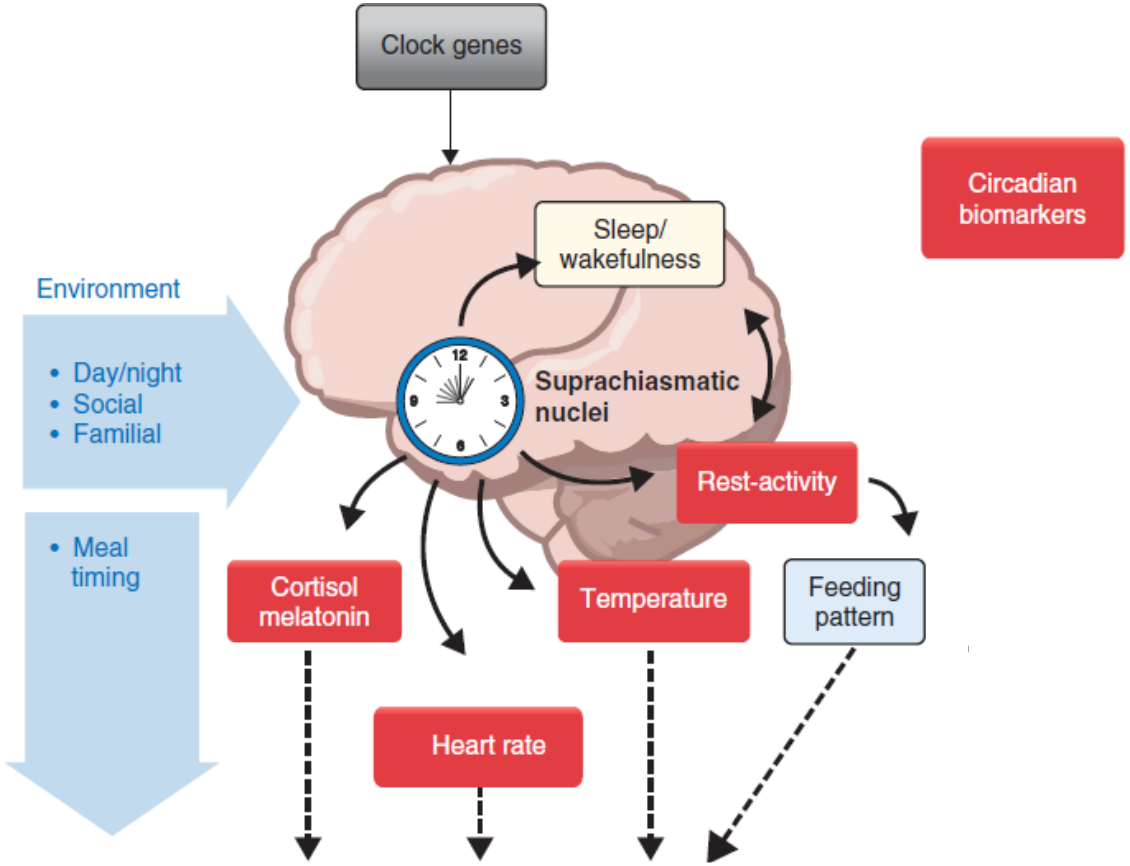


Clock on symptoms

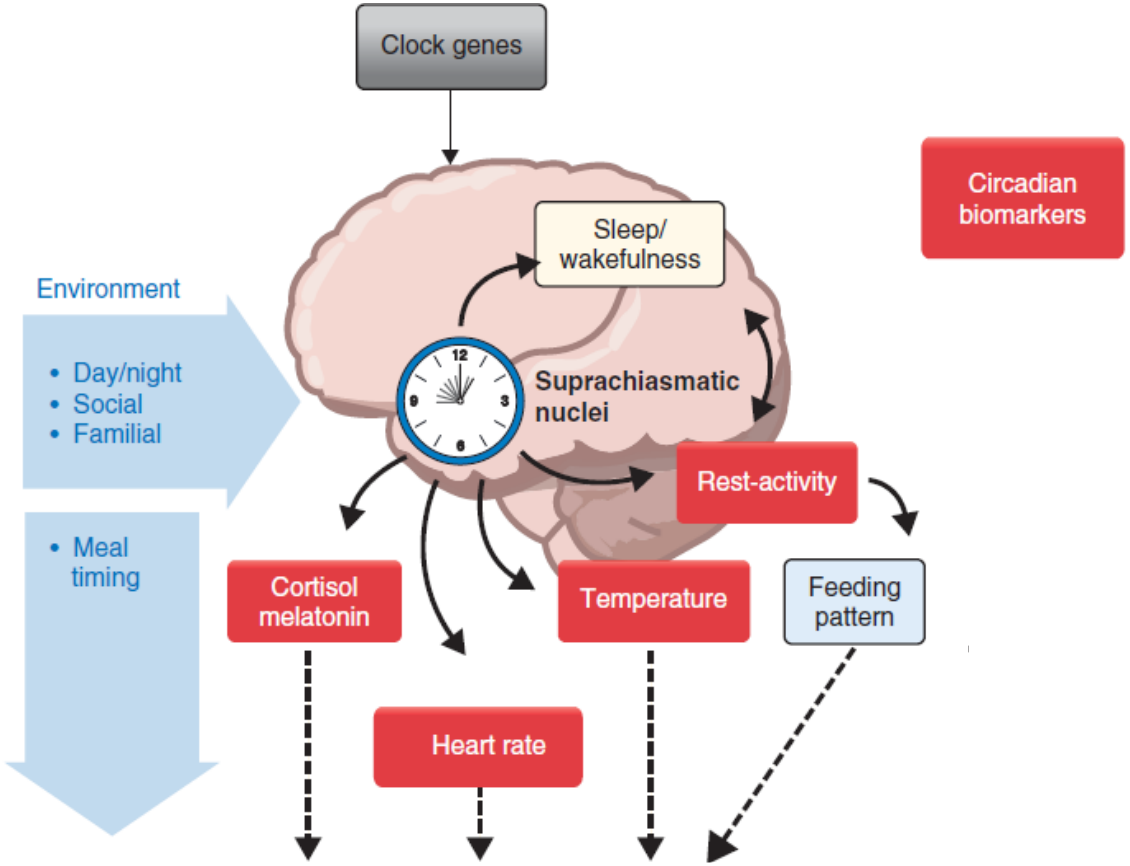


Awaiting 6:30 for resting…

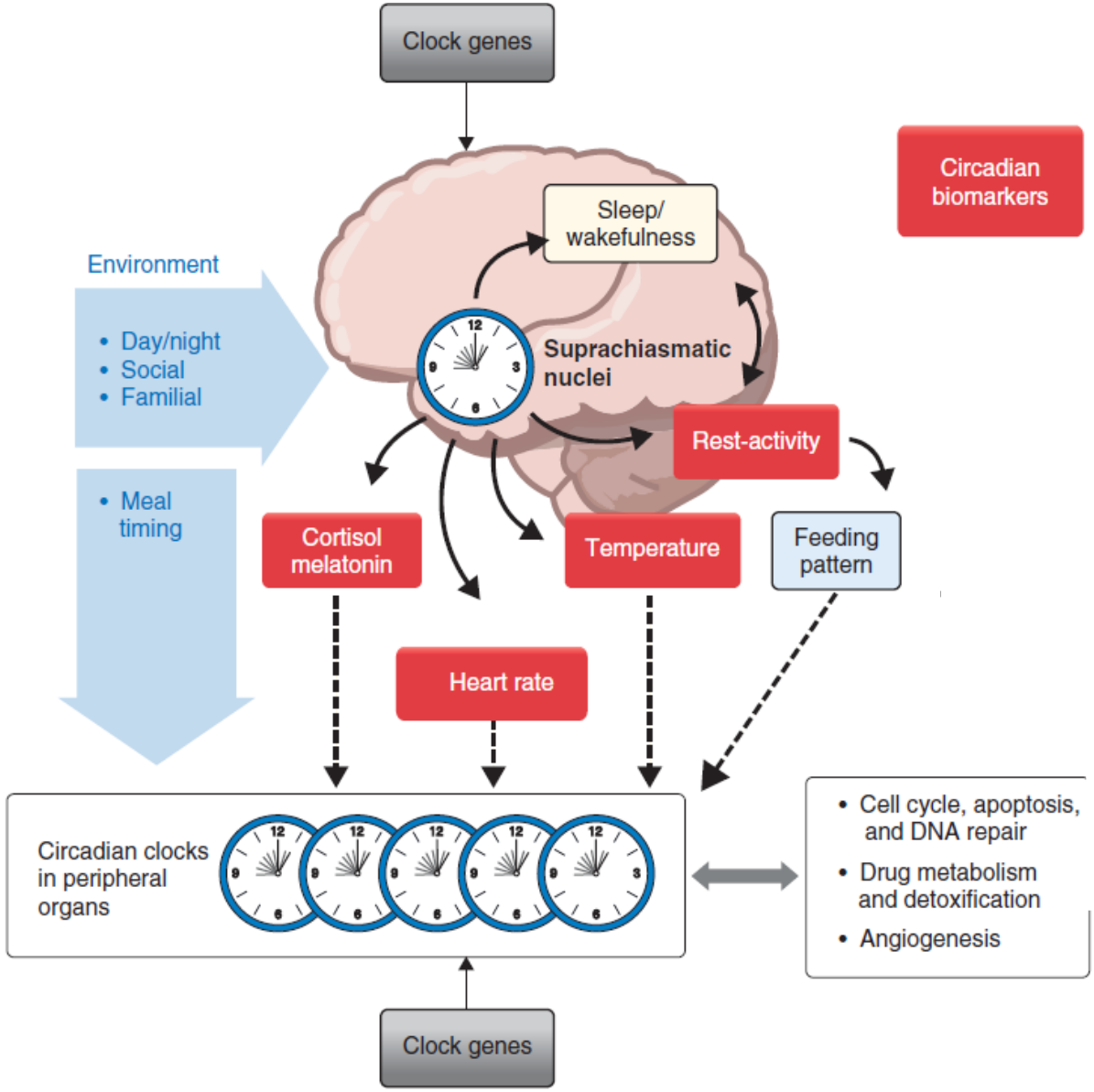
The Circadian Timing System



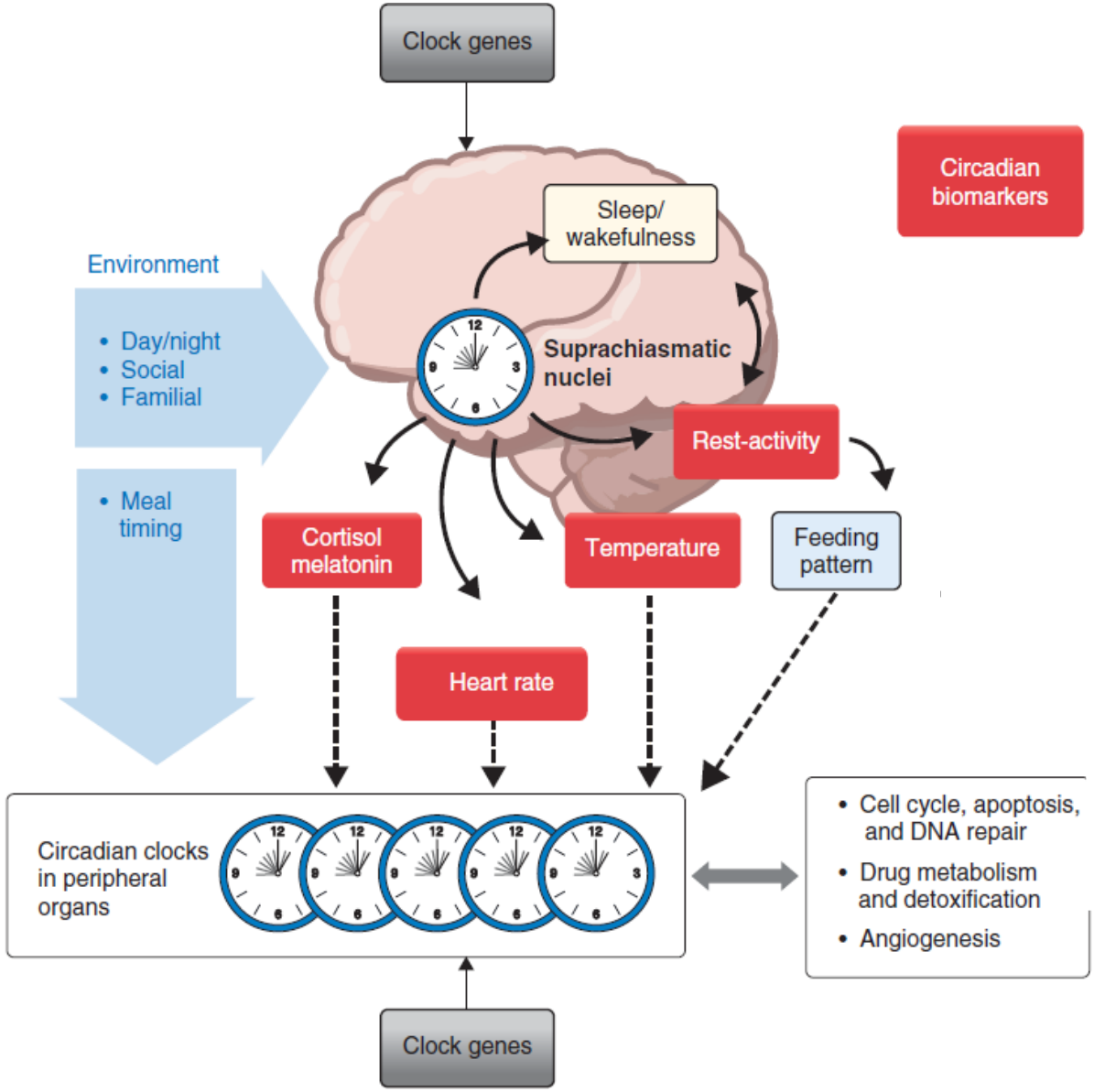
The Circadian Timing System

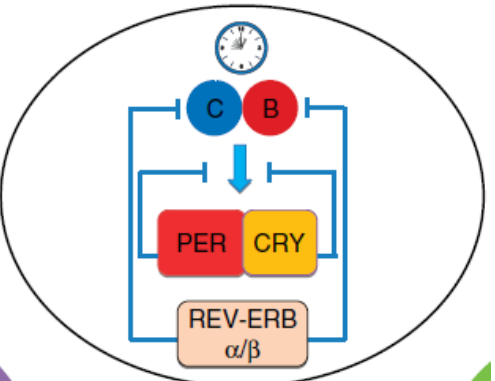


The Circadian Timing System

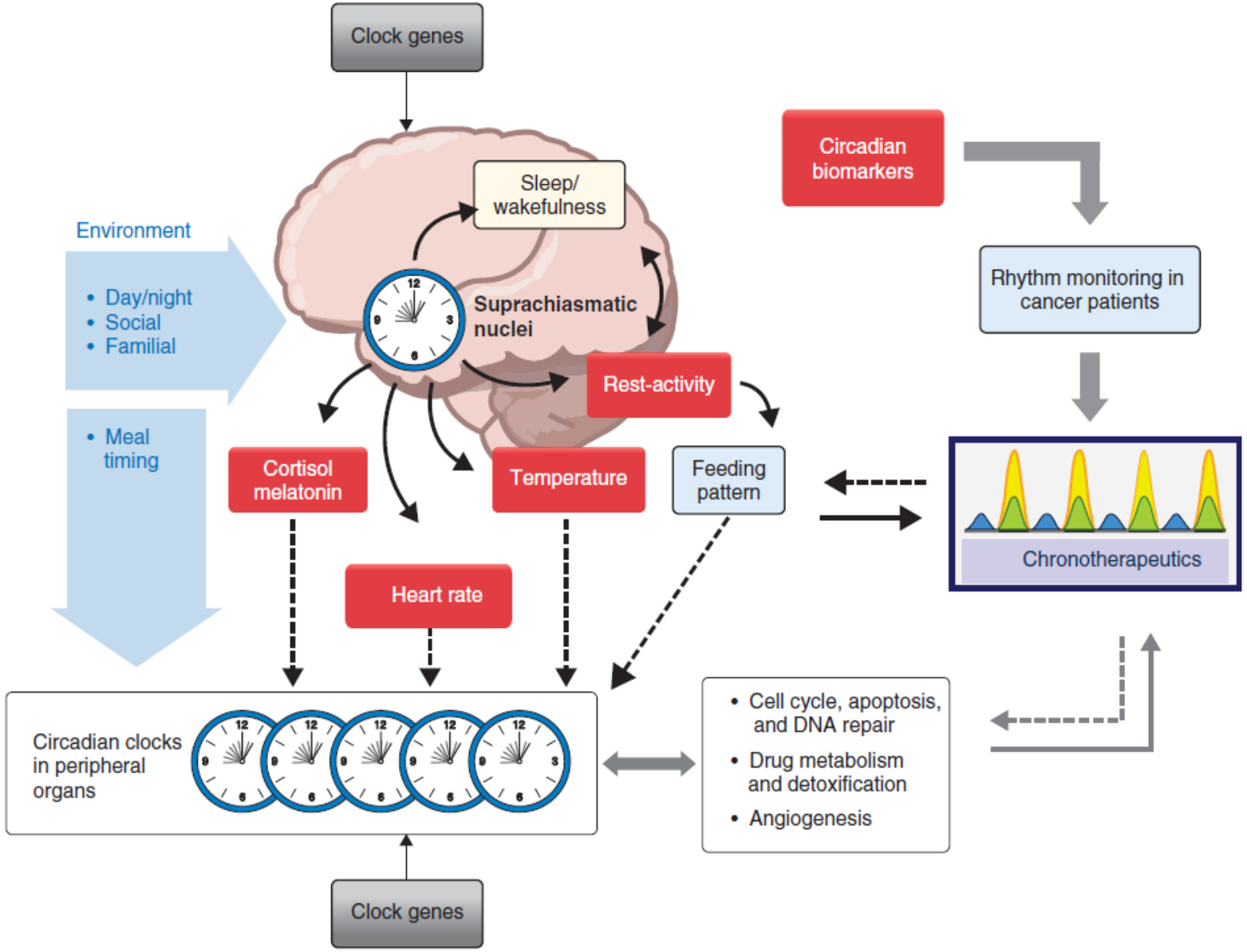


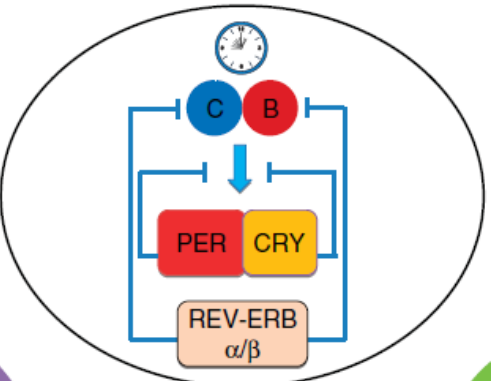
The Circadian Timing System



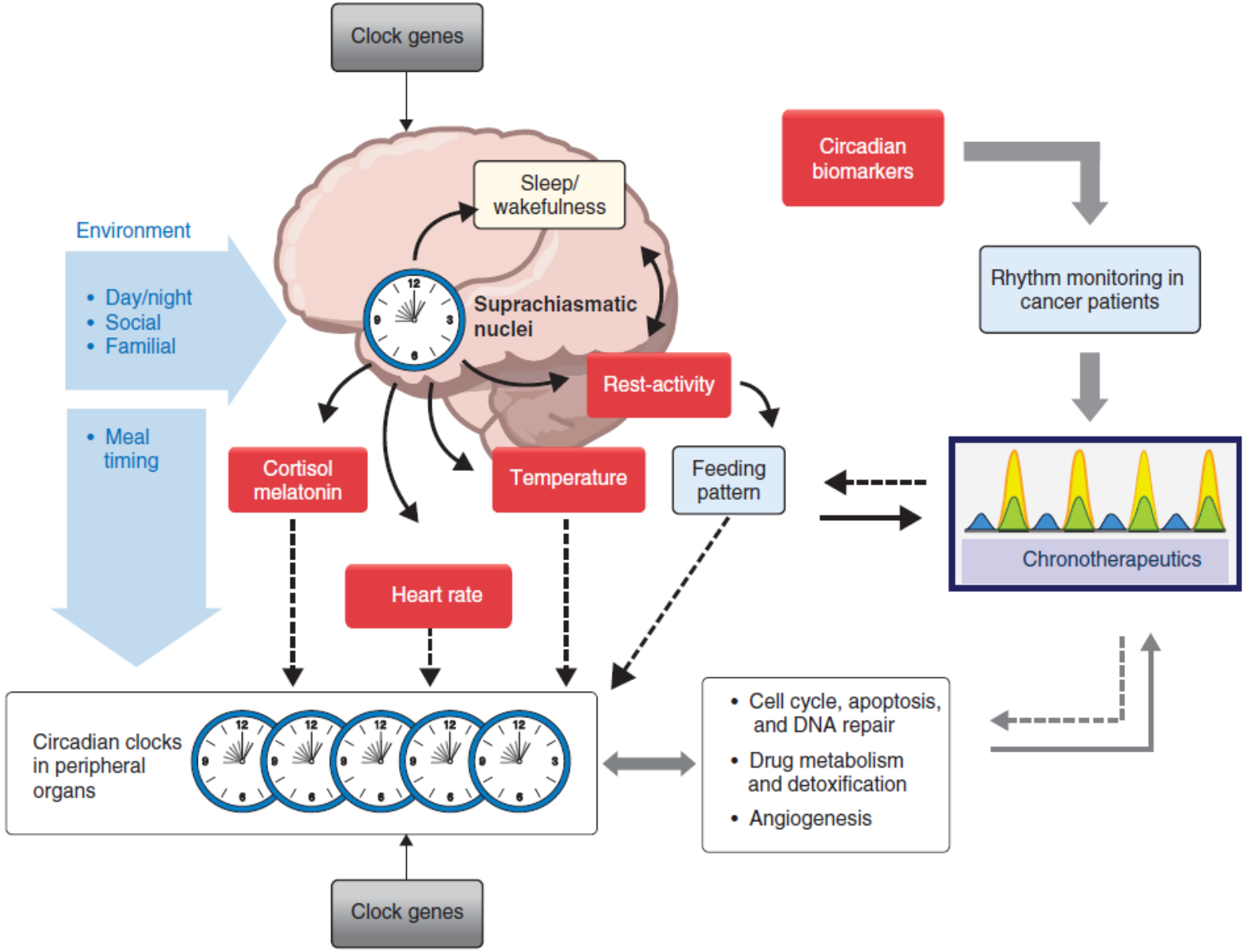


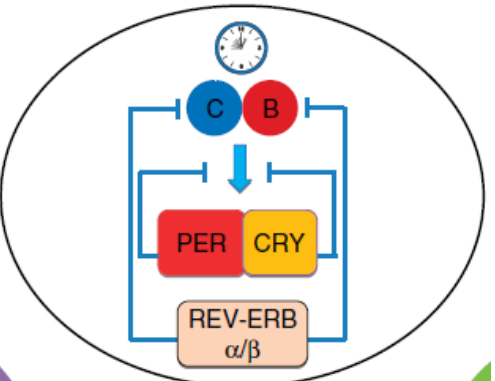
The Circadian Timing System





The Circadian Timing System





- Clock- Cell cycle coupling at single cell level
- Clock- Chronopharmacology at cell population level
- Cancer Chronopharmacology in mice
- Cancer Chronotherapy in patients
- Integration into home care

Systems Cancer Chronotherapeutics

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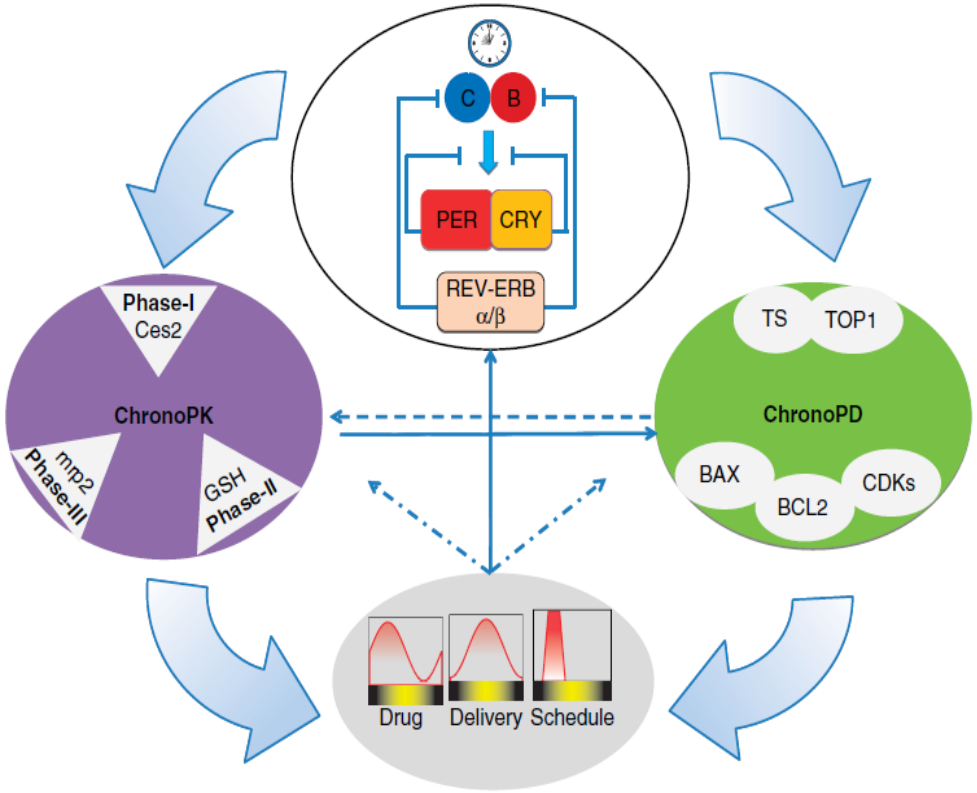
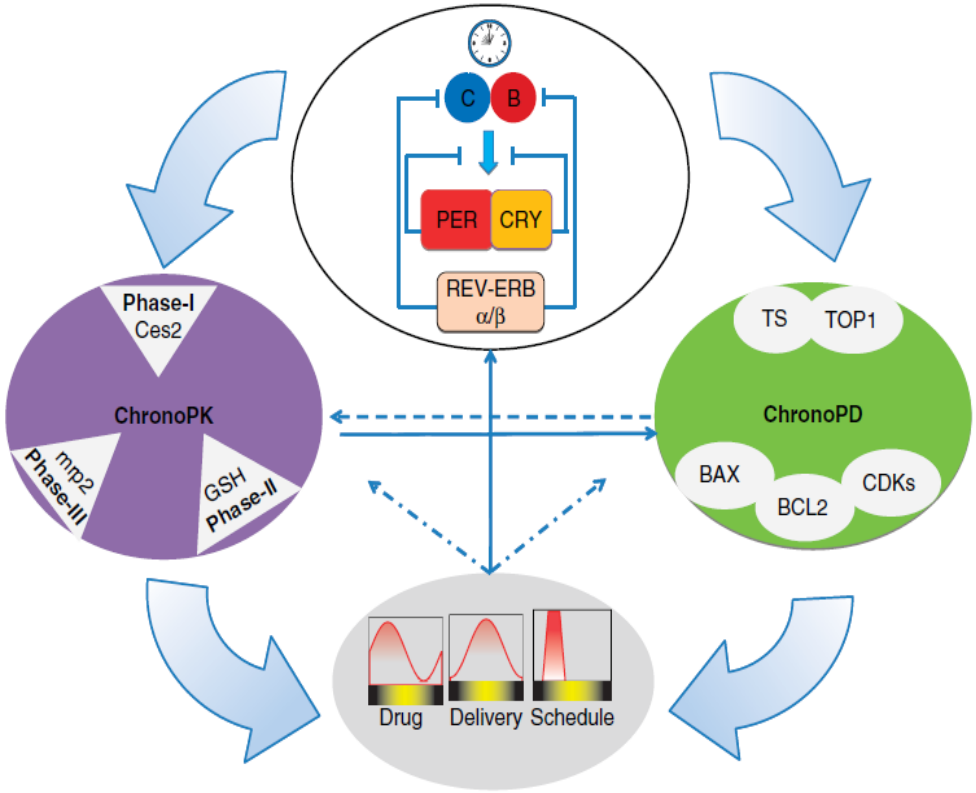
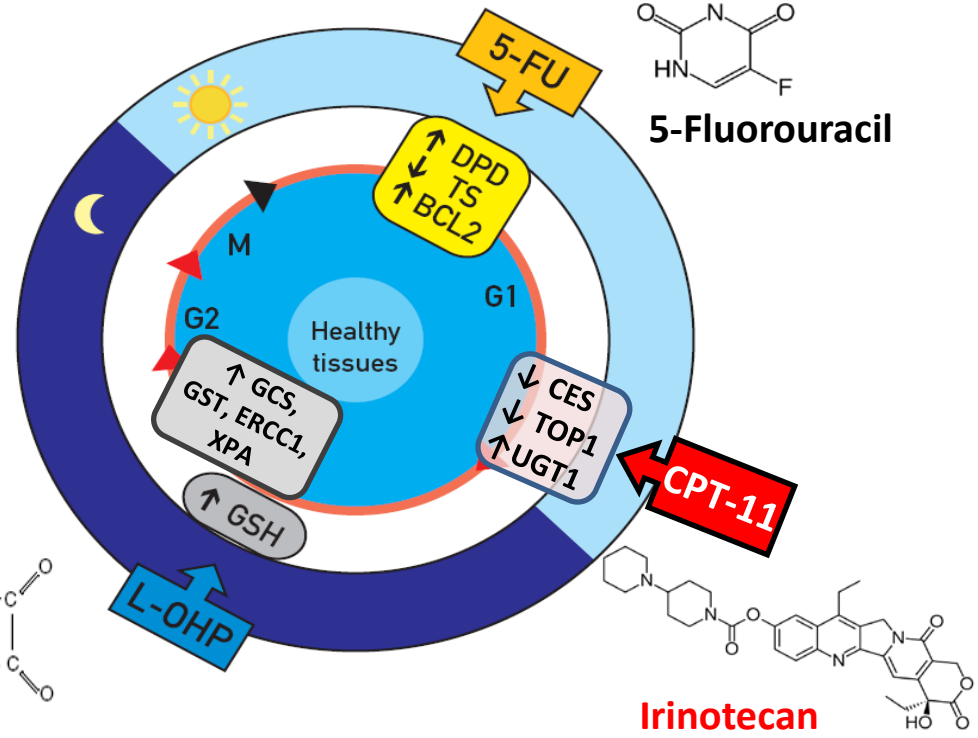
Systems Cancer Chronotherapeutics



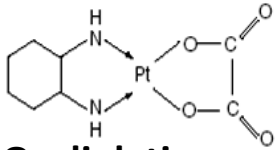
Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010

Systems Cancer Chronotherapeutics





5-Fluorouracil

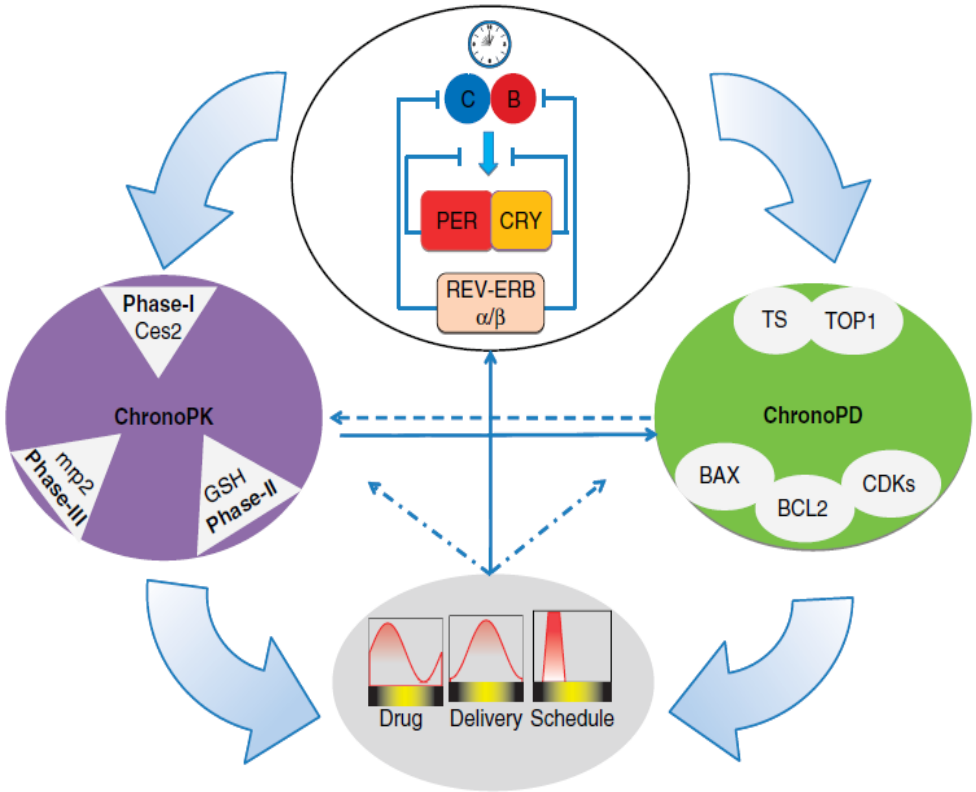


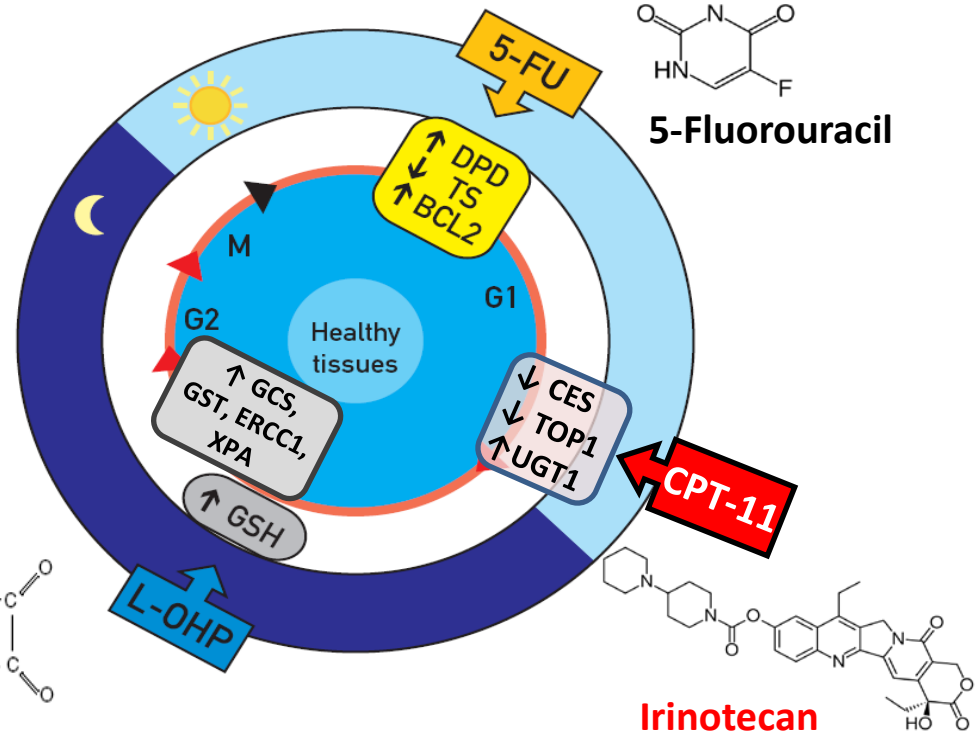
Oxaliplatin

Irinotecan

Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010

Systems Cancer Chronotherapeutics





5-Fluorouracil

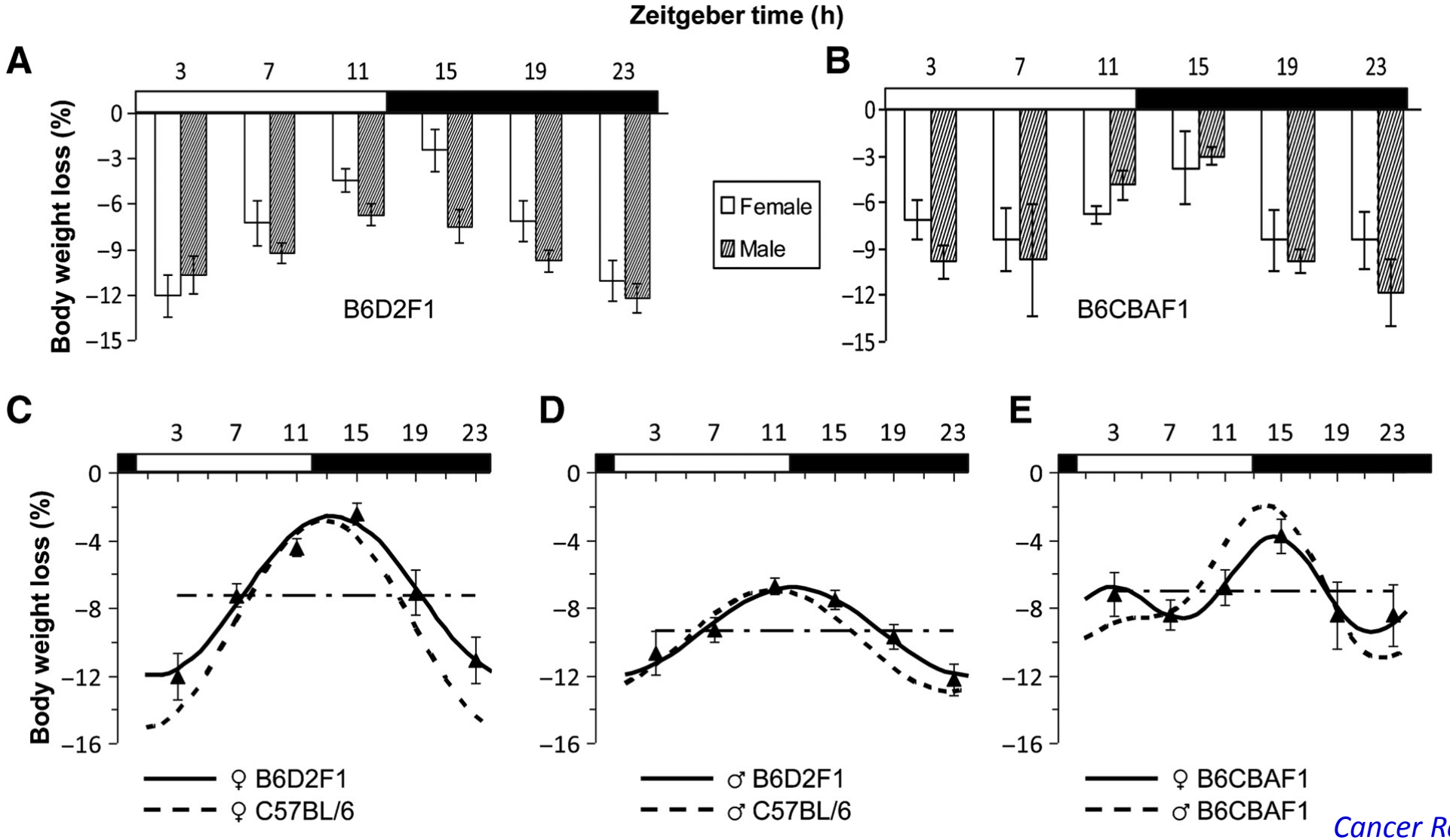
Oxaliplatin

Irinotecan

Chronotolerance
40 anticancer drugs
Chronoefficacy
28 anticancer drugs

Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010

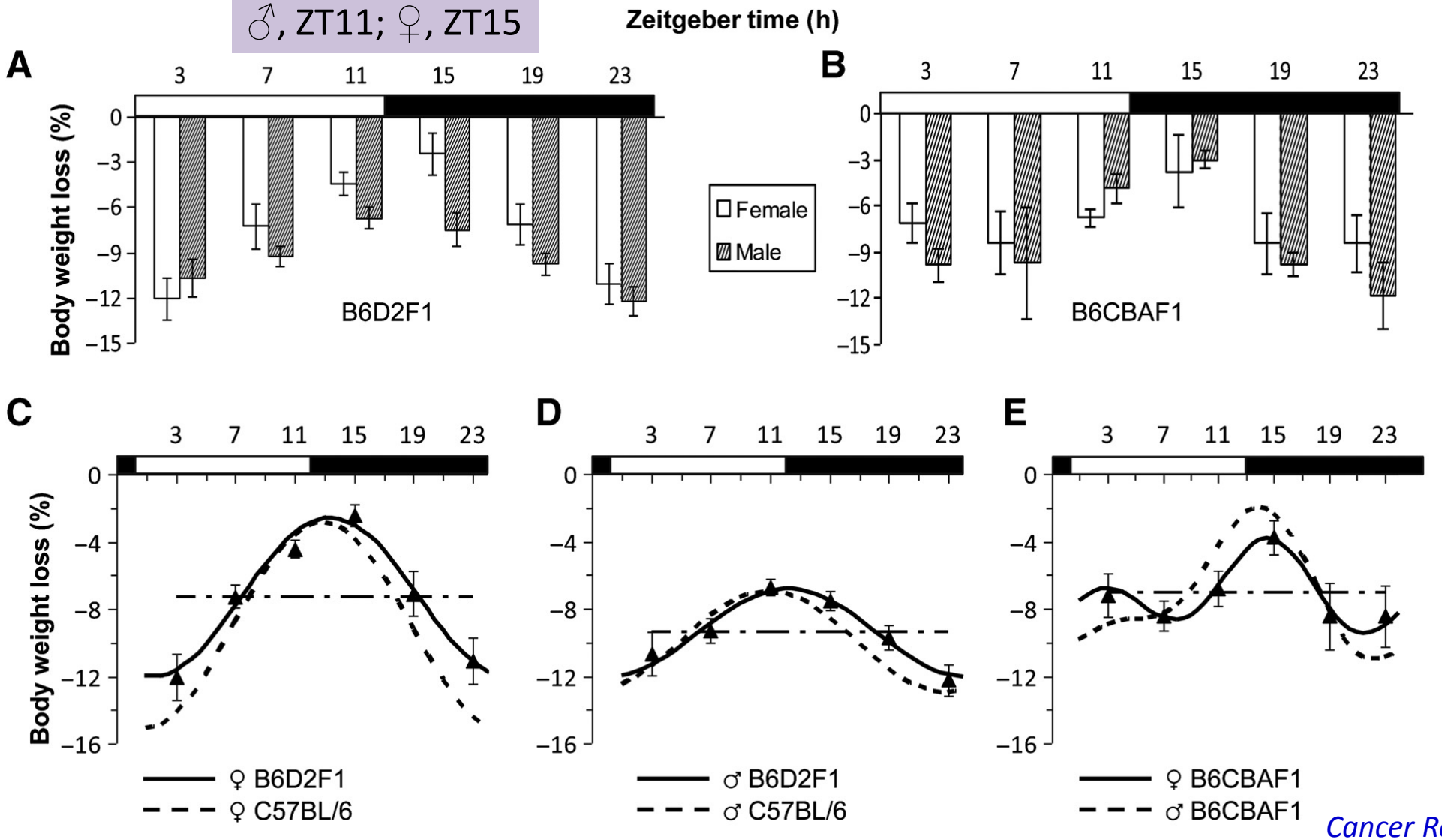
Sex and genetic differences in irinotecan chronotolerance in mice : 3 classes



Li et al.
Cancer Res 2013

Sex and genetic differences in irinotecan chronotolerance in mice : 3 classes

♂, ZT11; ♀, ZT15

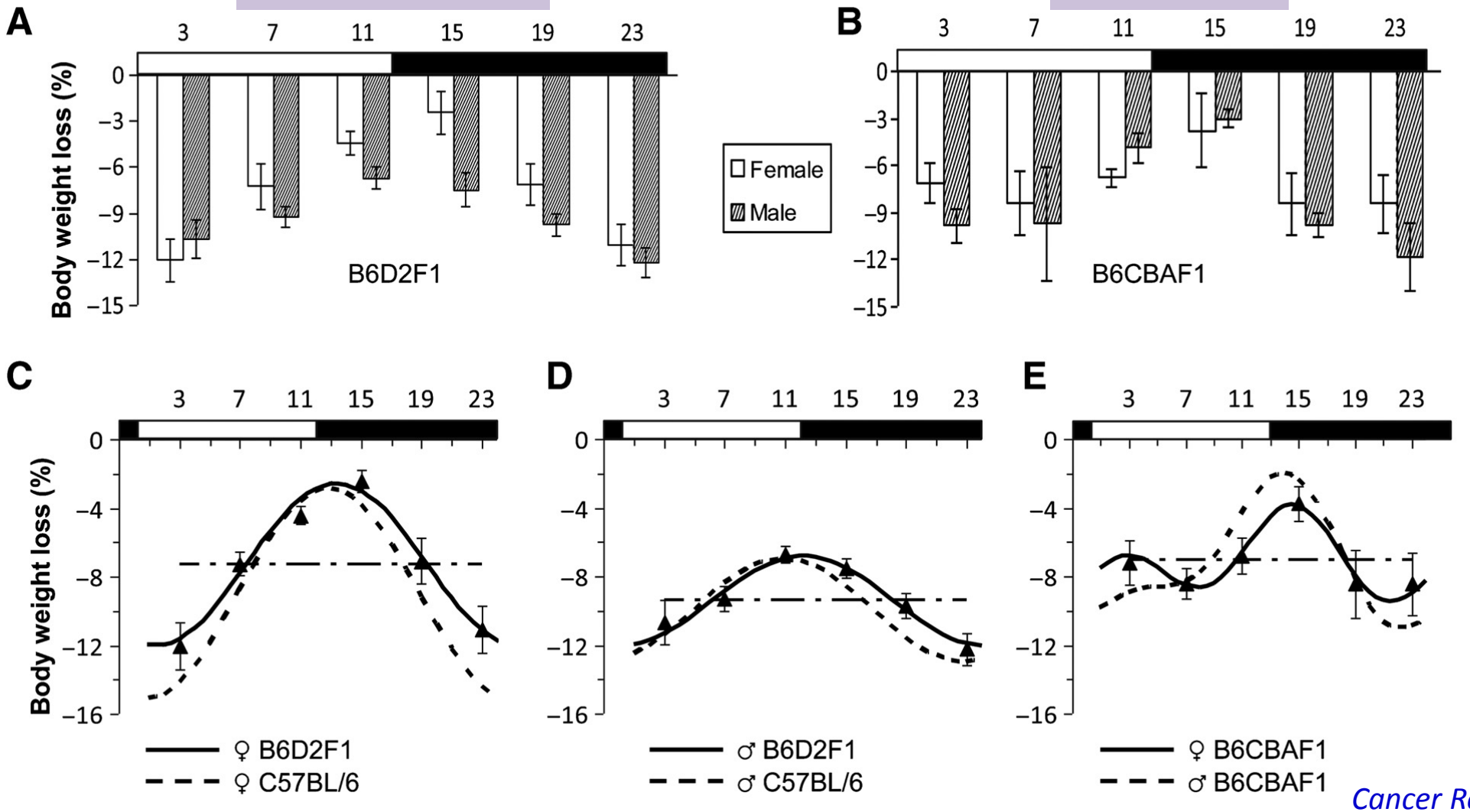


Li et al.
Cancer Res 2013

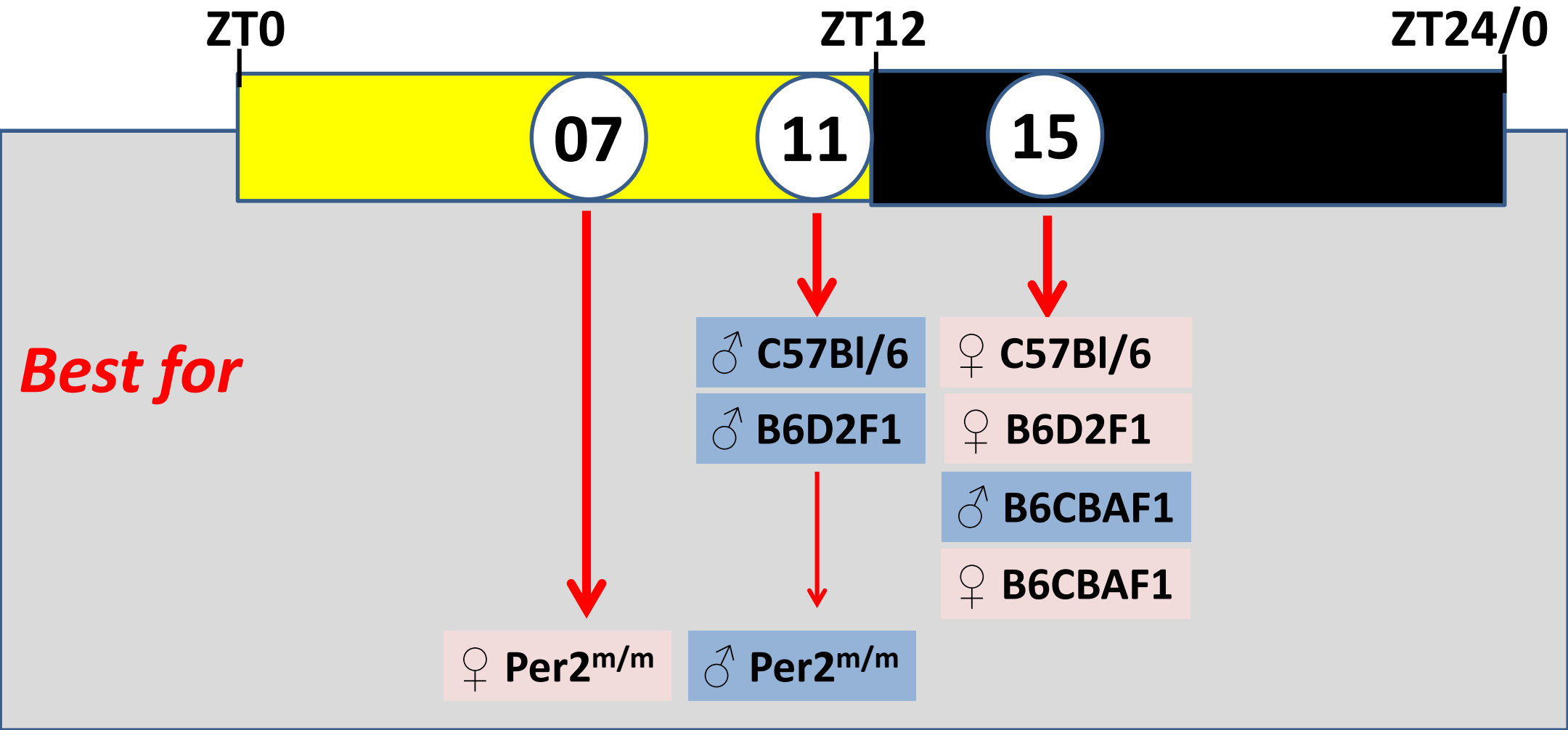
Sex and genetic differences in irinotecan chronotolerance in mice : 3 classes

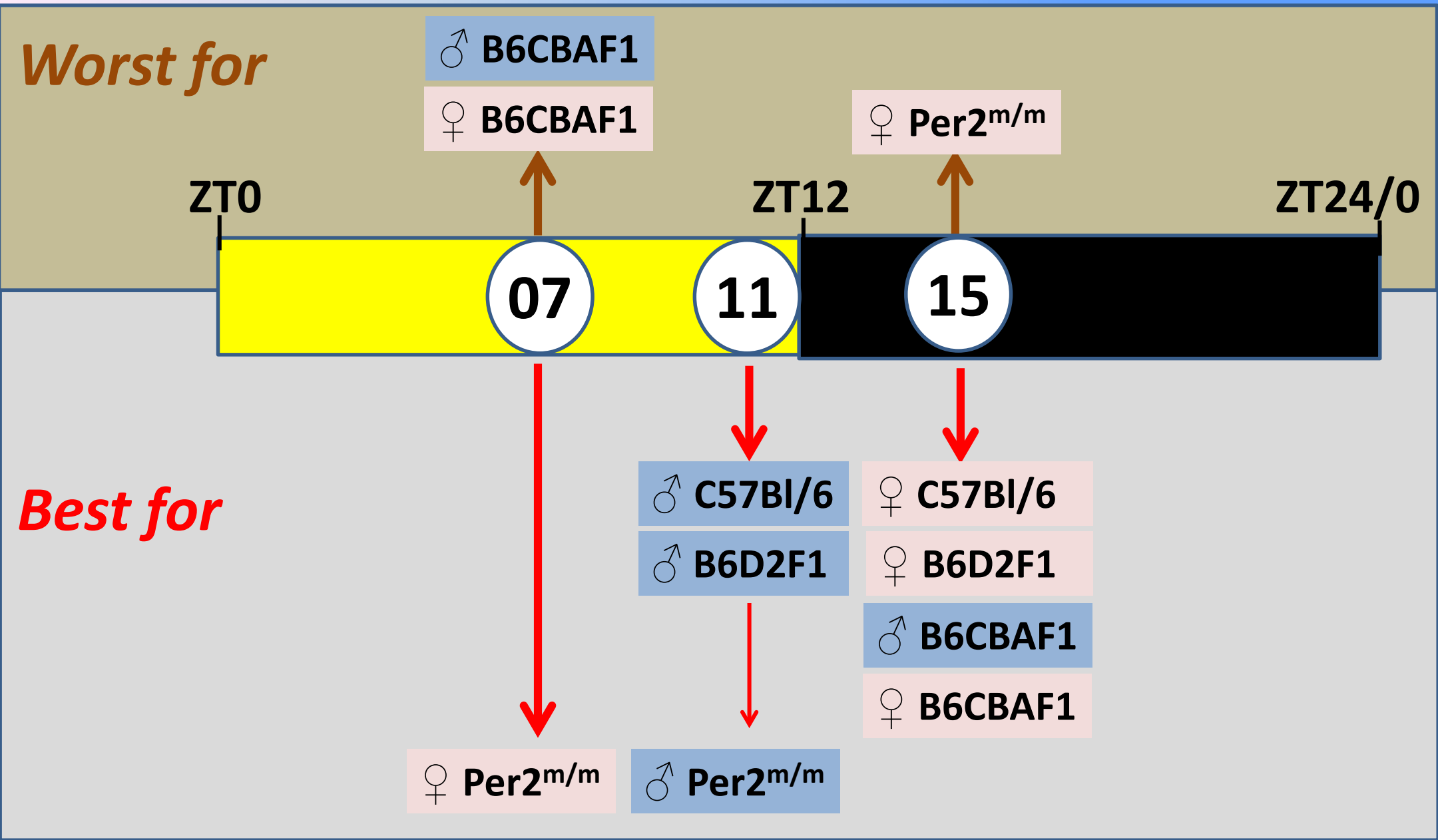
♂, ZT11; ♀, ZT15

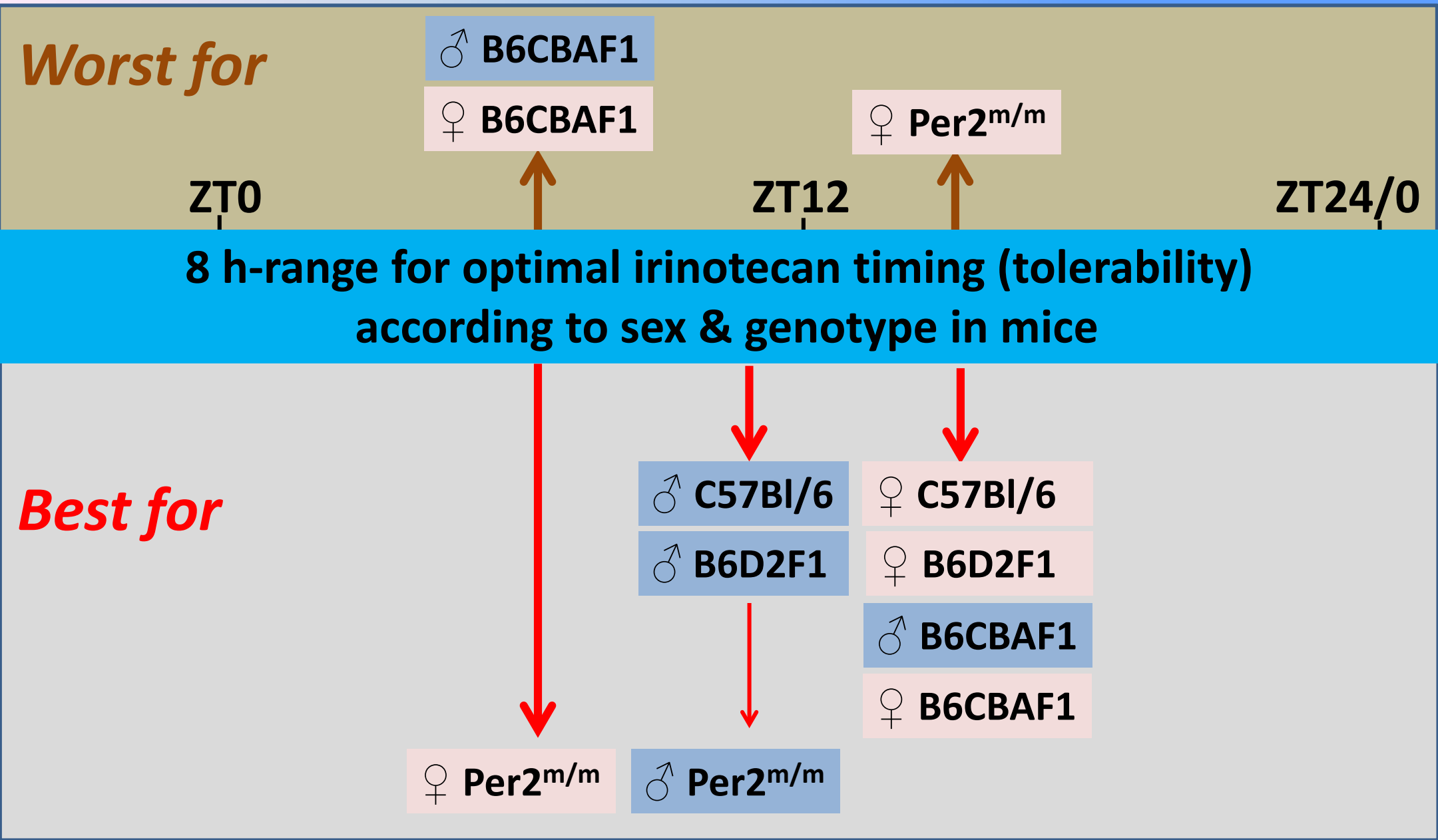
♂ & ♀, ZT15



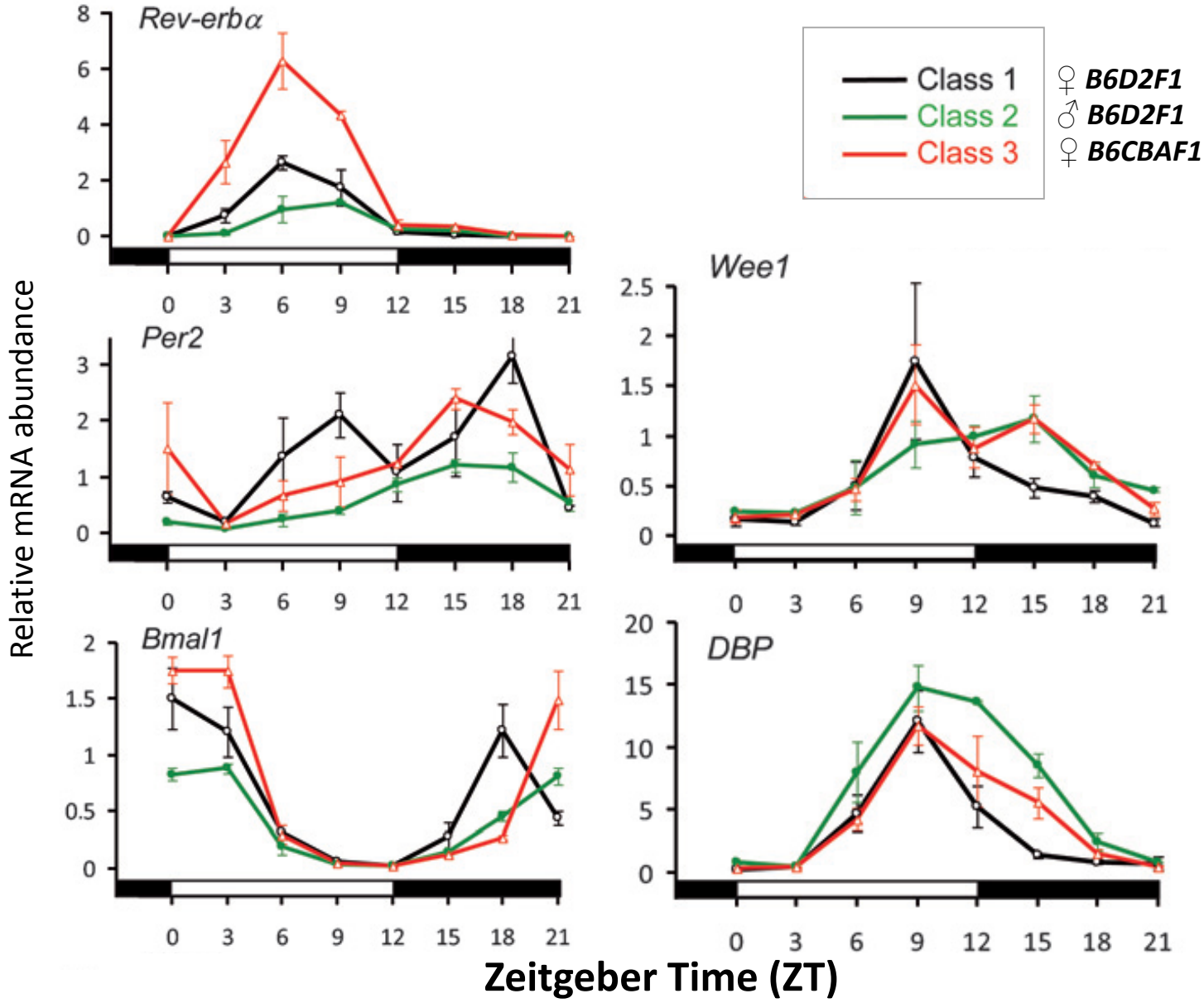
Li et al.
Cancer Res 2013


ZT0
ZT12
ZT24/0
07
11
15
Best for
♂ C57Bl/6
♀ C57Bl/6
♂ B6D2F1
♀ B6D2F1
♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m
♂ Per2m/m


Worst for
♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m
ZT0
ZT12
ZT24/0
07
11
15
Best for
♂ C57Bl/6
♂ B6D2F1
♀ C57Bl/6
♀ B6D2F1
♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m
♂ Per2m/m


Worst for
♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m
ZT0
ZT12
ZT24/0
8 h-range for optimal irinotecan timing (tolerability)
according to sex & genotype in mice
Best for
♂ C57Bl/6
♀ C57Bl/6
♂ B6D2F1
♀ B6D2F1
♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m
♂ Per2m/m

Sex and genetic differences in circadian clock & clock-controlled gene transcription in mouse liver



Li et al. Cancer Res 2013

8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Which of 27 liver or colon circadian gene transcription patterns predict for optimal timing if any?

Li et al. Cancer Res 2013

Systems Cancer Chronotherapeutics

Xiao Mei Li

8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Elisabeth Filipski

Which of 27 liver or colon circadian gene transcription patterns predict for optimal timing if any?

V Hossard

M Dumitru

Li et al. Cancer Res 2013

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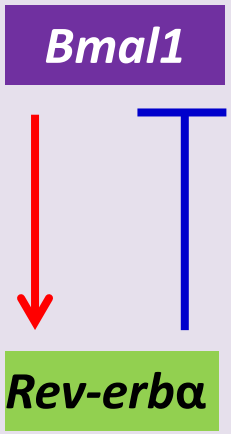

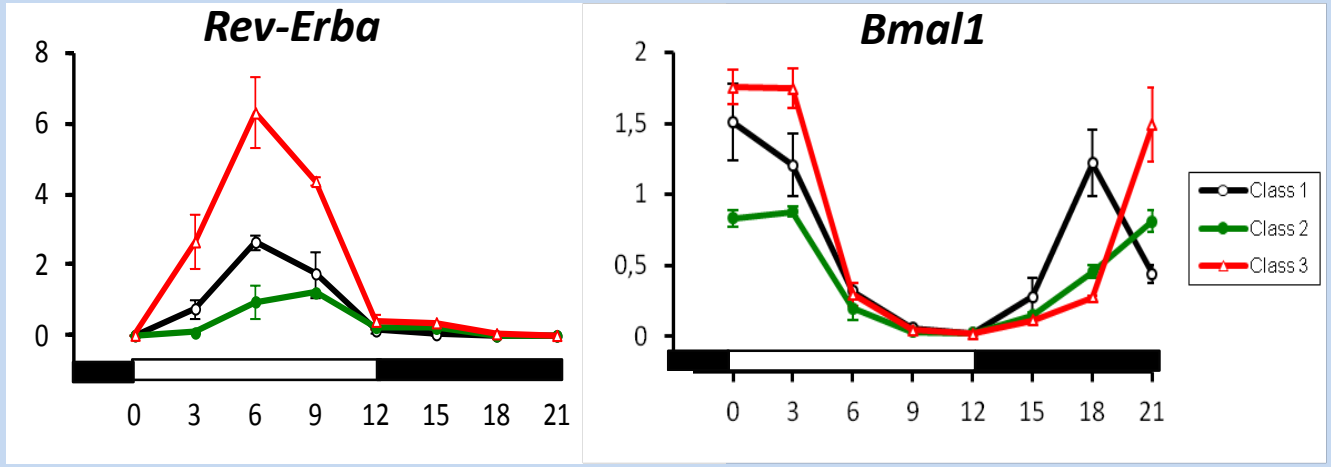

Li et al. Cancer Res 2013

Systems Cancer Chronotherapeutics

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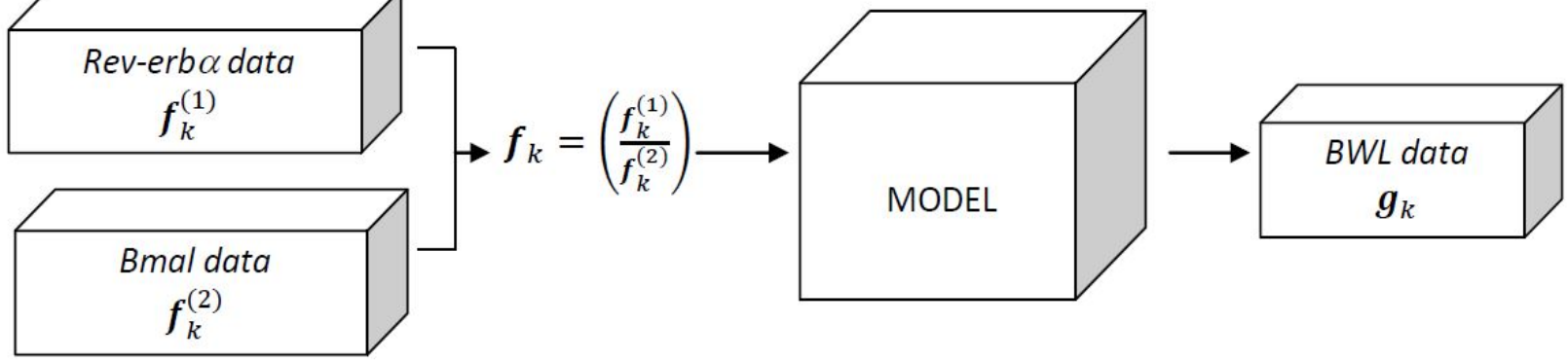
8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Elisabeth Filipski

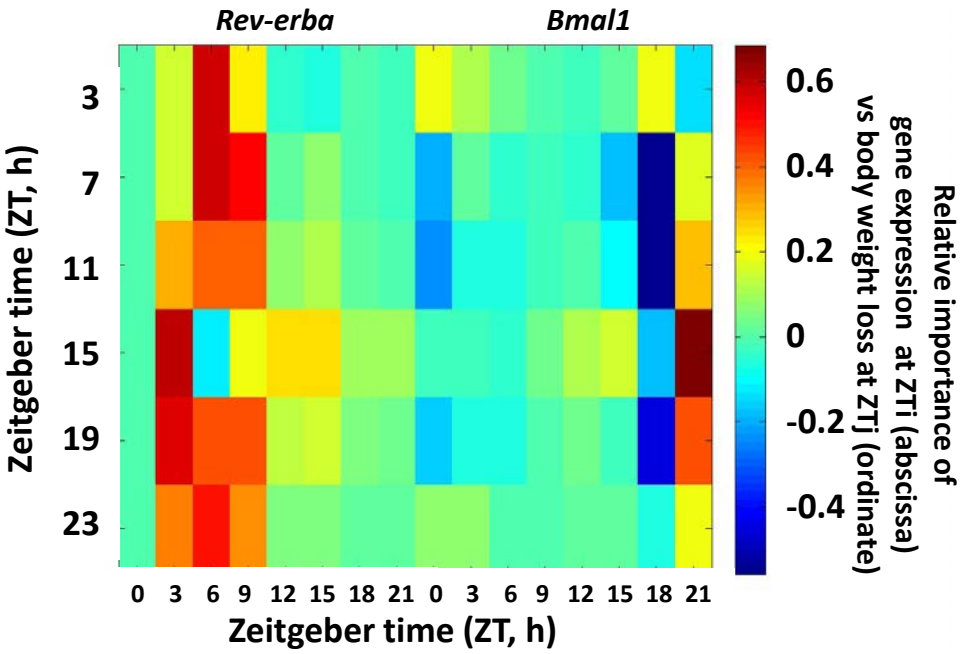
Ali Mohammad-Djafari (CNRS, SUPELEC, Paris Sud Univ)

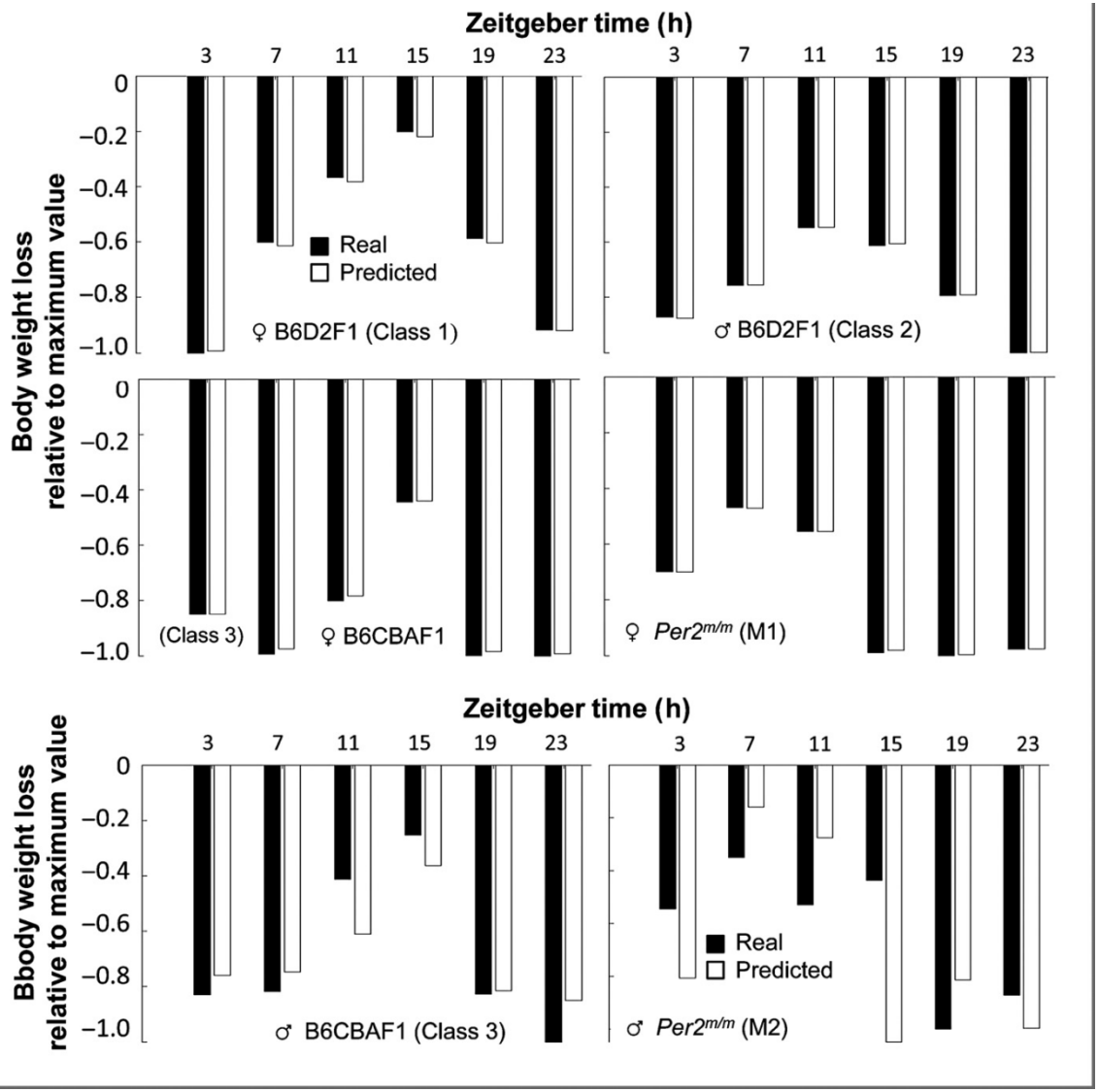


A circadian clock transcription model for the personalization of cancer chronotherapy timing

Li et al. Cancer Res 2013

A circadian clock transcription model for the personalization of cancer chronotherapy





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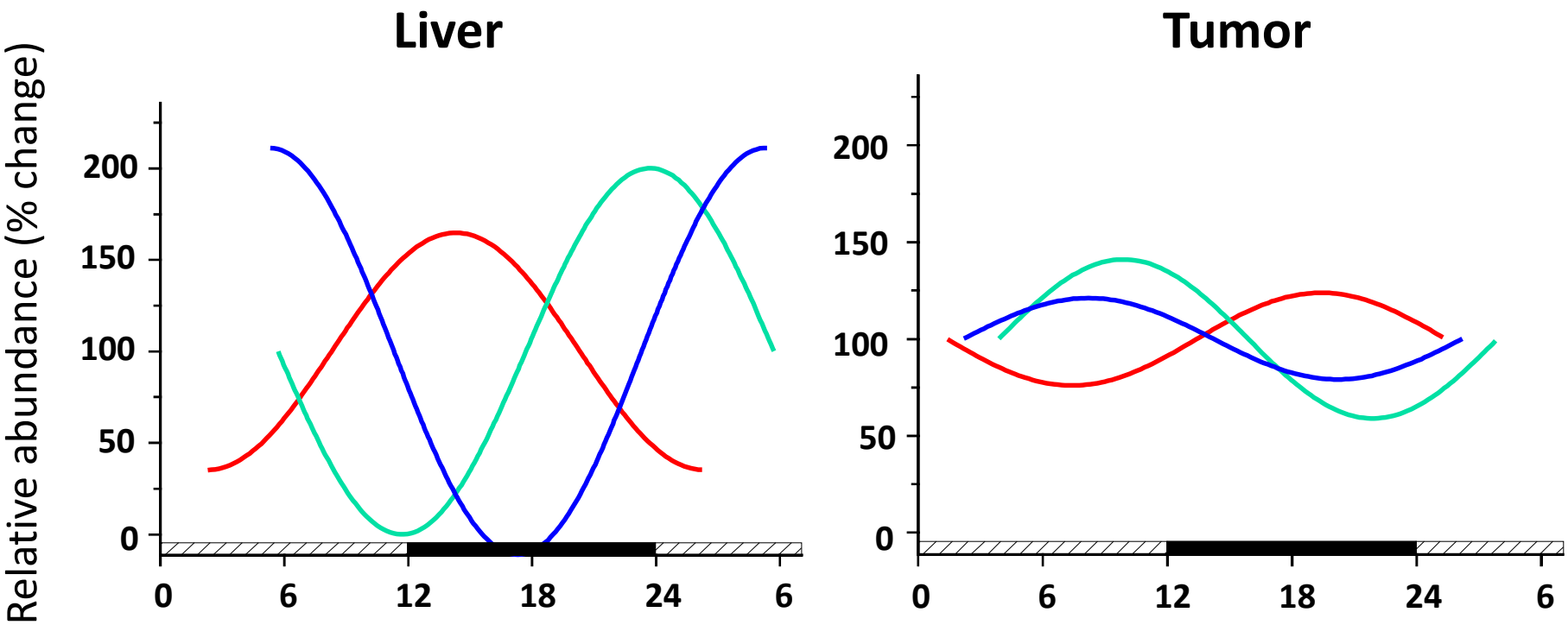
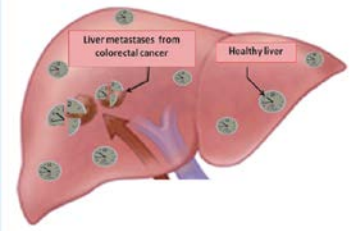

Liver
Tumor
Relative abundance (% change)
200
150
100
50
0
0
6
12
18
24
6
Circadian Time (hours , referred to light onset)
mRNA transcription
Rev-erbα
Per2
BMal1

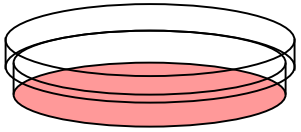
Systems Cancer Chronotherapeutics

Systems Cancer Chronotherapeutics



- **Systematic exploration of role of clock genes in liver and cancers for cell cycle, drug metabolism and chronotherapeutic effects**
- **Continuous physiology monitoring & dynamic molecular imaging**

Per2::luc/Bmal1::luc
± si/shRNA
Rev-Erbα-FUCCI



Lumicycle

Per2::luc
Abcb1a::luc

Clock mutant
Cancer prone

RT-Bio

IVIS Spectrum

Systems Cancer Chronotherapeutics

- Clock- Cell cycle coupling at single cell level
- Clock- Chronopharmacology at cell population level
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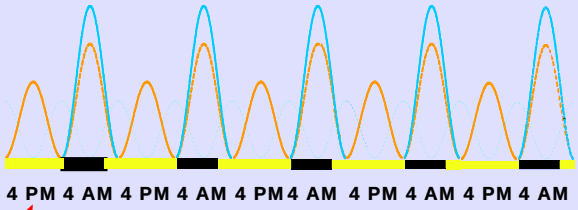
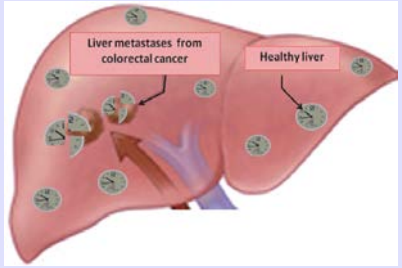
Curative intent onco-surgery strategy in patients with metastatic colorectal cancer

1986-2013

Chronotherapy

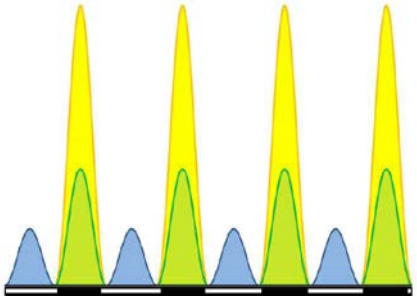




Liver resection & transplantation

Oxaliplatin

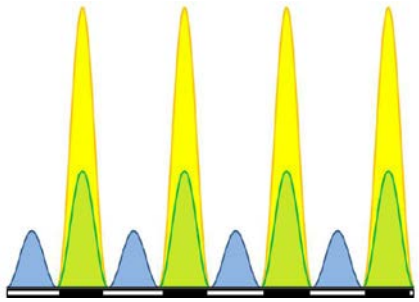
JNCI 1990, 1994; Cancer 1992, 1999, 2009, 2013; Ann Surg 1996, 2004, 2010, 2011; Lancet 1997; Lancet Oncol 2001; Ann Oncol 1999, 2012; JCO 1996, 2000, 2006, 2007, 2008, 2009; IJC 2012, 2013.

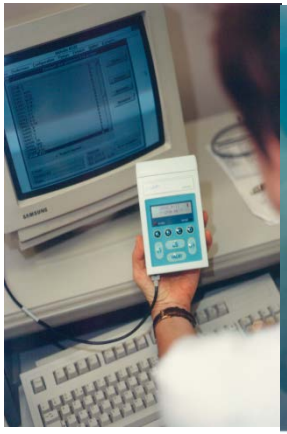


Research & Development

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients

Systems Cancer Chronotherapeutics





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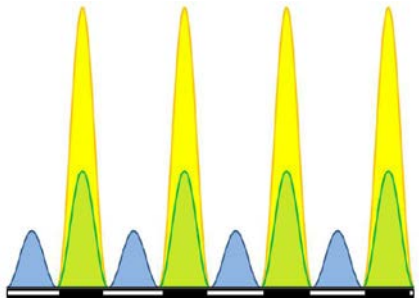
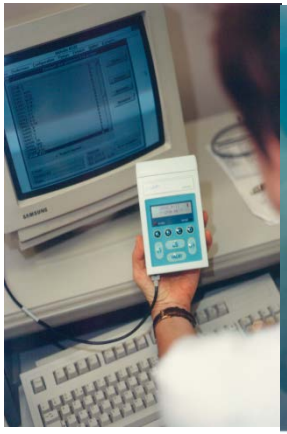




Research & Development

Oncologist — **Consultation** — **Patient**

Personnalized medical care plan
Prescription, verification

Home Care

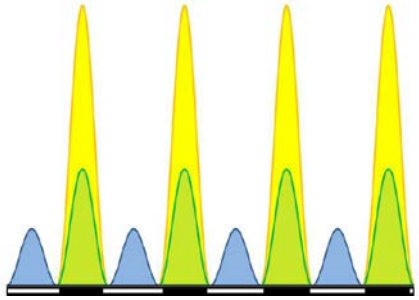
Coordination

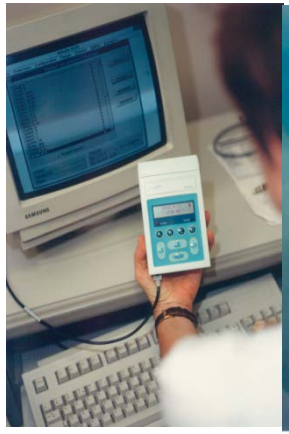
Programmation → **Pharmacy** → **Care Unit**

→ **Home**

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients

Systems Cancer Chronotherapeutics





Research & Development

Education
- **health care personnels**
- **patients**

Oncologist — **Consultation** — **Patient**

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Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
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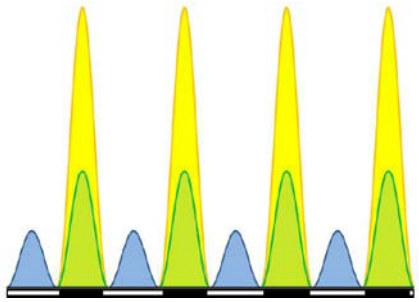
Systems Cancer Chronotherapeutics



Research & Development

Education
- health care personnels
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Oncologist — Consultation — Patient

Personnalized medical care plan
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Programmation → Pharmacy → Care Unit

Home Care

Family doctor

Home

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients

Chronotherapeutic trials with 5-FU-LV-oxaliplatin (1988-2006)

Trial	Schedule	Gr 3-4 toxicity (% pts)	Objective responses (%)
Phase III 278 pts, 1st line	**Chrono-std**	**14%**	**51%**
		P<0.001	***P=0.003***
	Constant	76%	30%
Phase I-II staggered 114 pts 2-3rd line	**Chrono-std**	**16%**	**30%**
	Chrono-std ±12h	80%	12%

Lévi et al. JNCI 1994; Lancet 1997; Lancet Oncol 2001; Adv Drug Deliv Rev 2007

Chronotherapeutic trials with 5-FU-LV-oxaliplatin (1988-2006)

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	Constant	76%	30%
Phase I-II staggered 114 pts 2-3rd line	**Chrono-std: best tolerability consistent in men, not in women**		

Lévi et al. JNCI 1994; Lancet 1997; Lancet Oncol 2001; Adv Drug Deliv Rev 2007

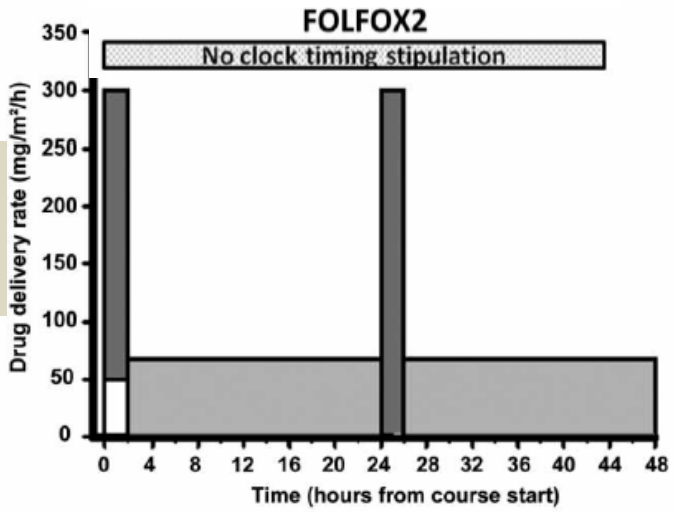
Survival improvement in men on chronoFLO for metastatic colo-rectal cancer (meta-analysis of 3 randomized international trials in 842 patients)

Sex (N patients)	Drug delivery schedule	Median survival, months [95% CL]	% alive at 5 years	P *(Logrank)*
Women (N = 345)	Chrono	16.6 [13.9-19.0]	8	0.012
	Conventional	18.4 [16.6-20.2]	21	
Men (N=497)	Conventional	17.5 [16.1-18.8]	18	0.009
	Chrono	**20.8 [18.7-22.9]**	**29**	

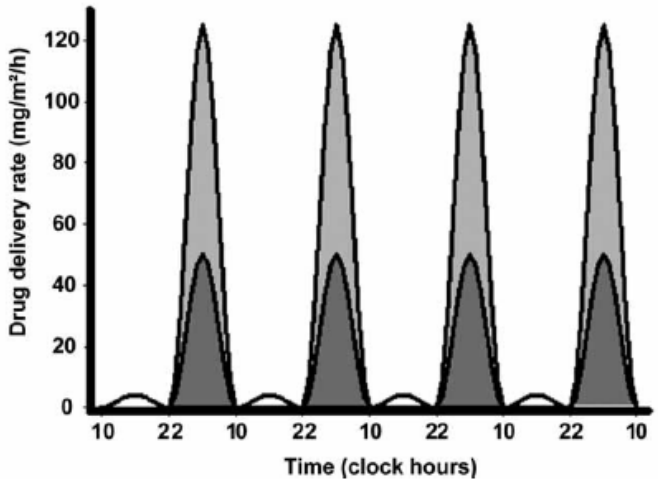
Giacchetti et al. Ann Oncol 2012

Systems Cancer Chronotherapeutics

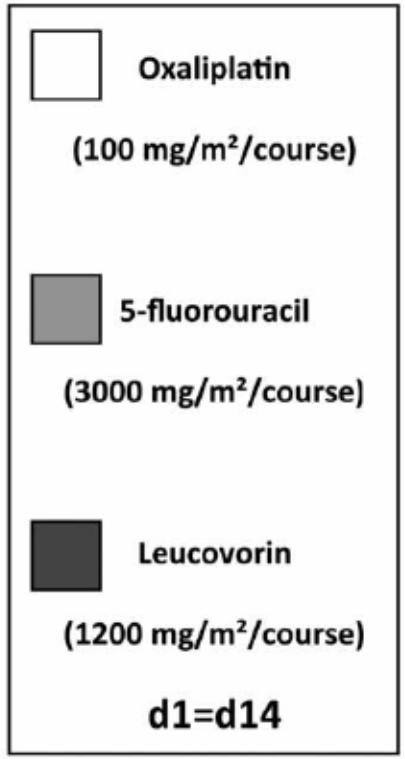
Conventional chemotherapy



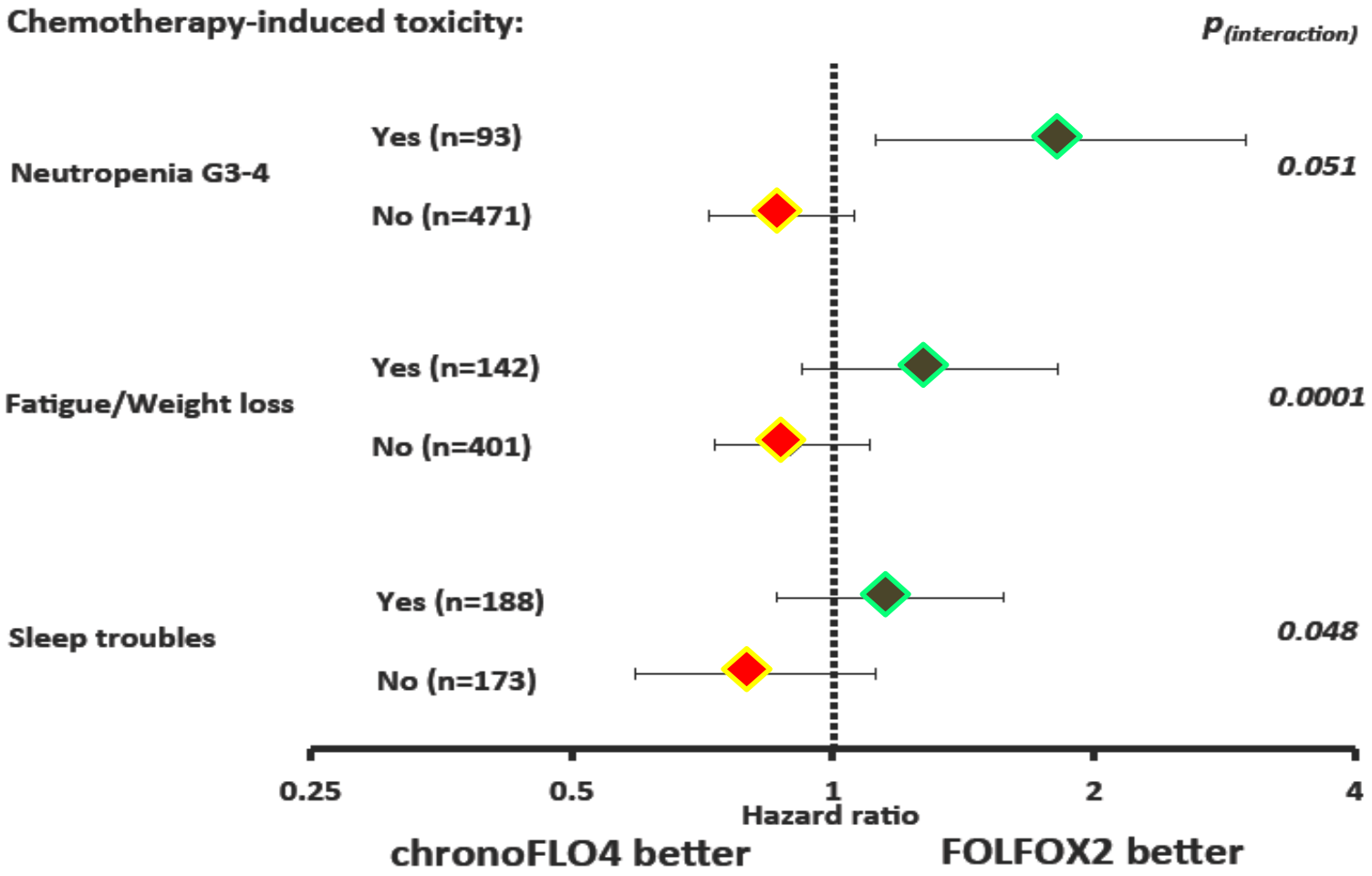
564 patients
first line treatment for metastatic colorectal cancer
36 centers, 10 countries



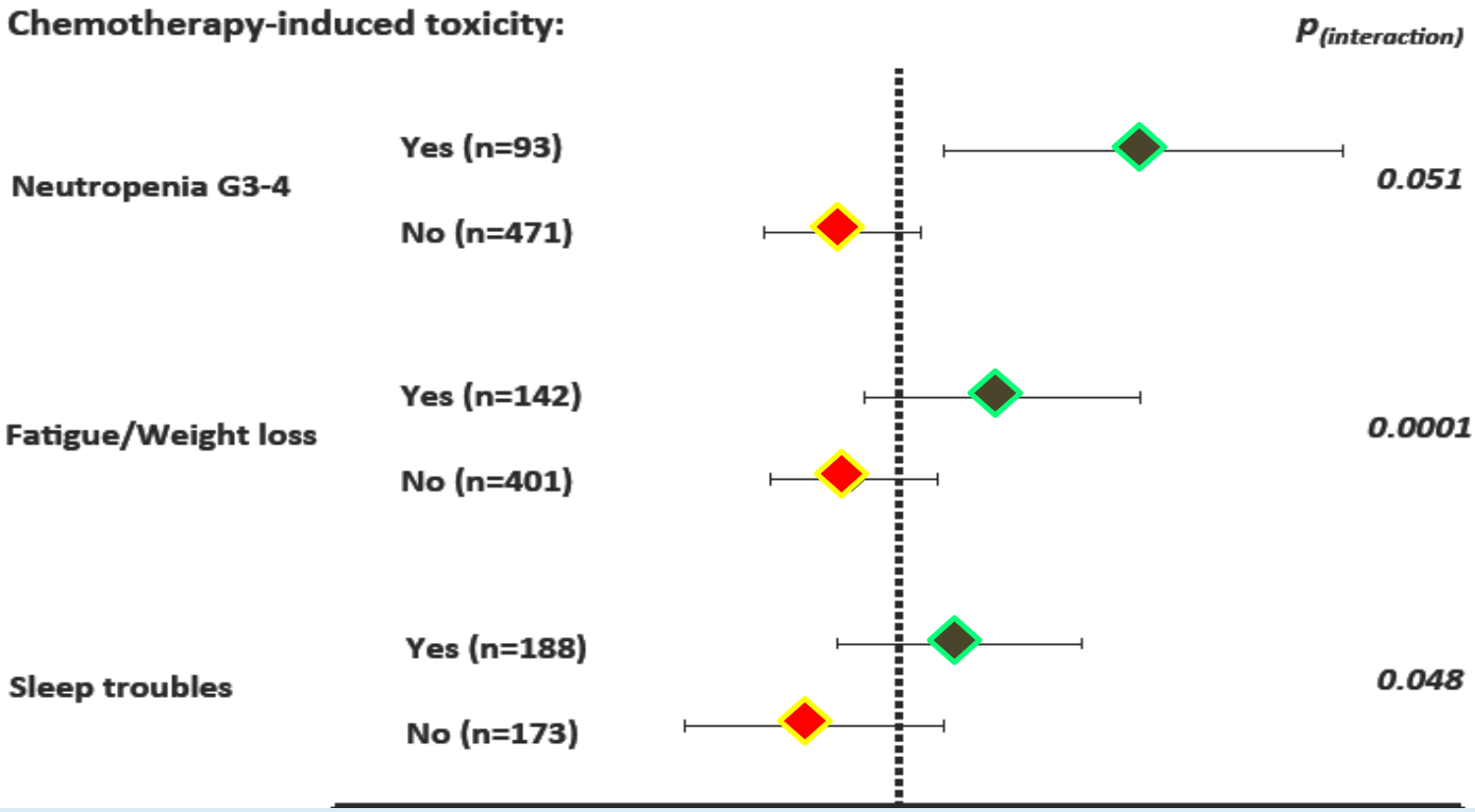
Chronotherapy



Giacchetti et al. J Clin Oncol 2006;
Ann Oncol 2012
Innominato et al. Chronobiology Int 2011
Int J Cancer 2012; Cancer 2013



Innominato et al. Chronobiology Int 2011
Int J Cancer 2012; Cancer 2013; Ann Med 2014, in press



Improved tolerability associated with improved survival on chronotherapy not on conventional FOLFOX

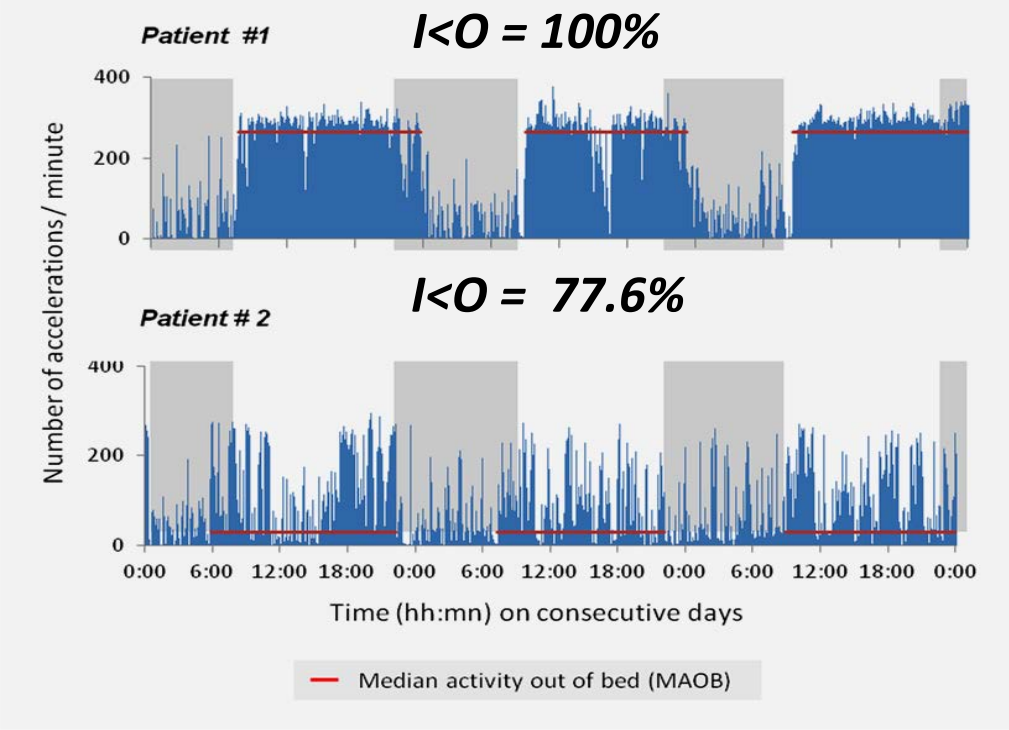
Innominato et al. Chronobiology Int 2011
Int J Cancer 2012; Cancer 2013; Ann Med 2014, in press

Clinical relevance of rest-activity rhythm

436 patients with metastatic colorectal cancer

Rest-activity monitoring

Computation of I<O



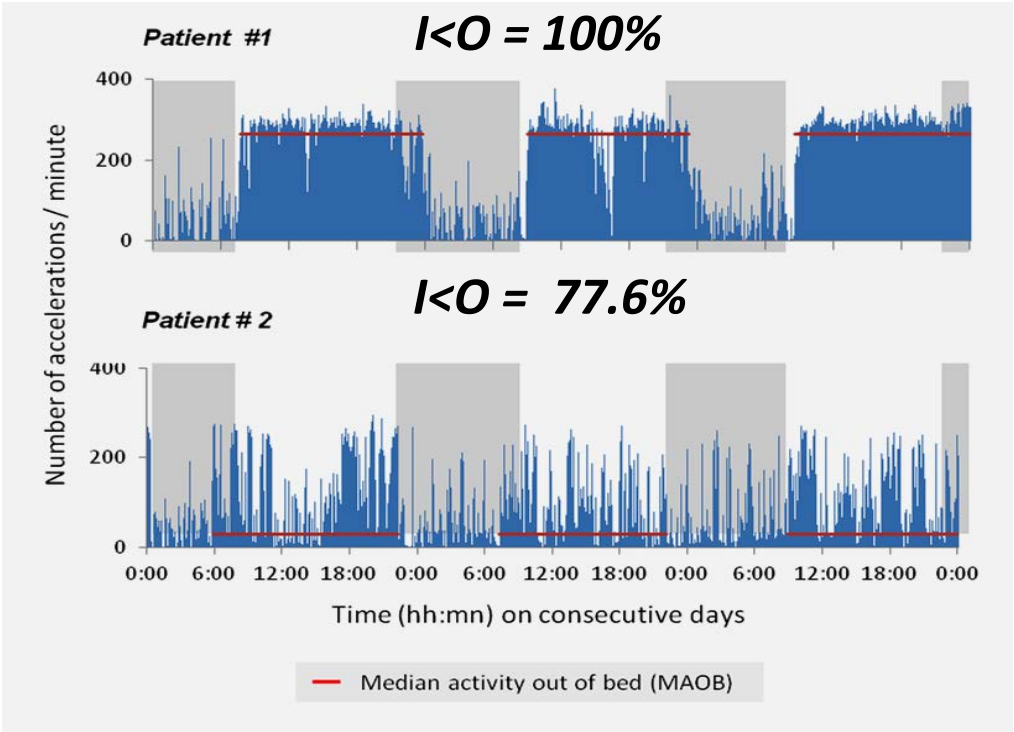
Circadian disruption: I<O less than 97.5%

Clinical relevance of rest-activity rhythm

436 patients with metastatic colorectal cancer

Rest-activity monitoring
Computation of I<O

I<O prediction of overall survival
in 436 patients



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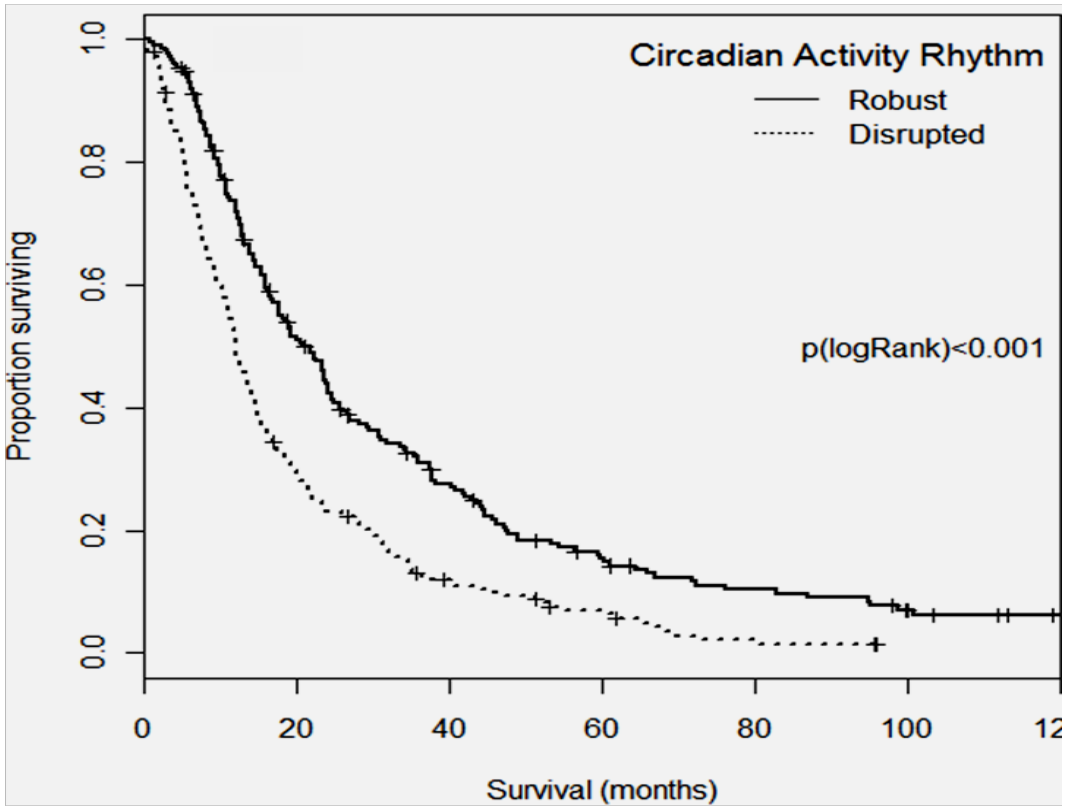


Lévi et al. Chronobiology Int 2014

Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

Circadian disruption on chemotherapy

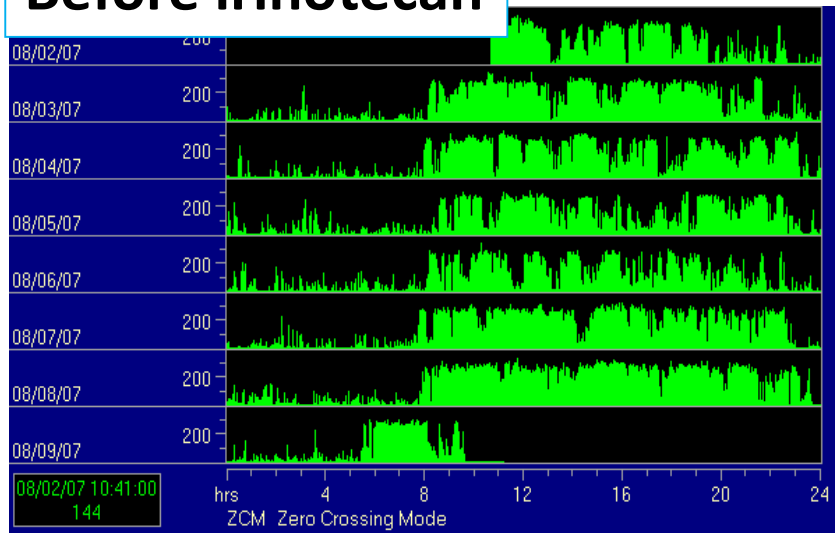
Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

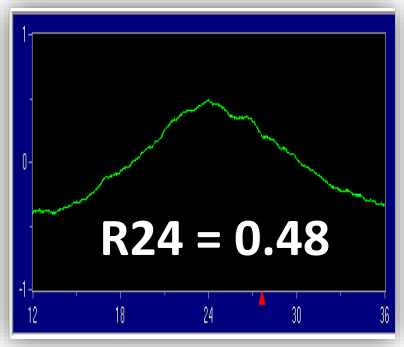
Motionlogger® Watch

Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

Before irinotecan





PS = 0

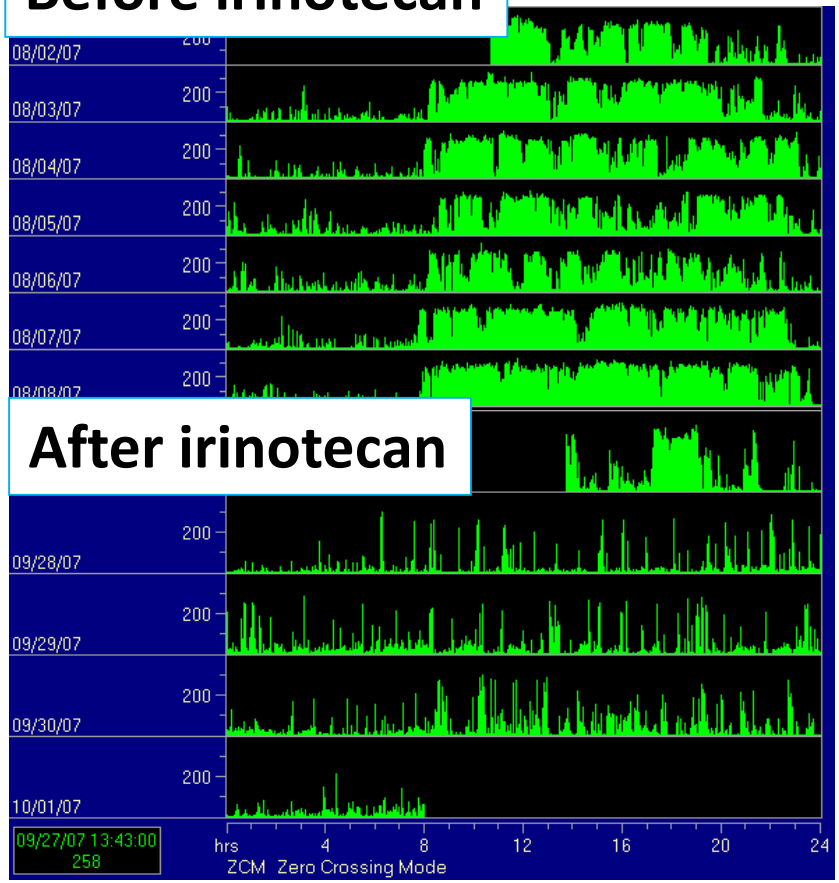
Motionlogger® Watch

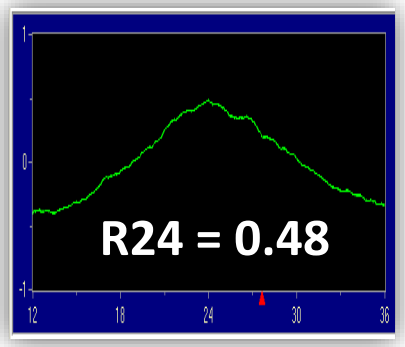
Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

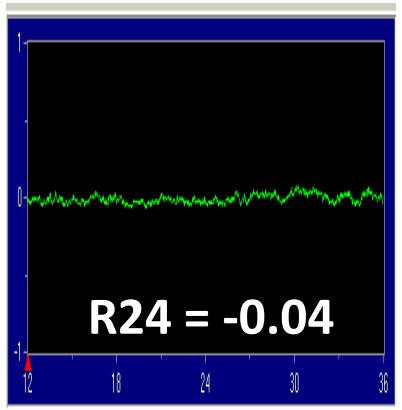
Motionlogger® Watch

Before irinotecan





PS = 0

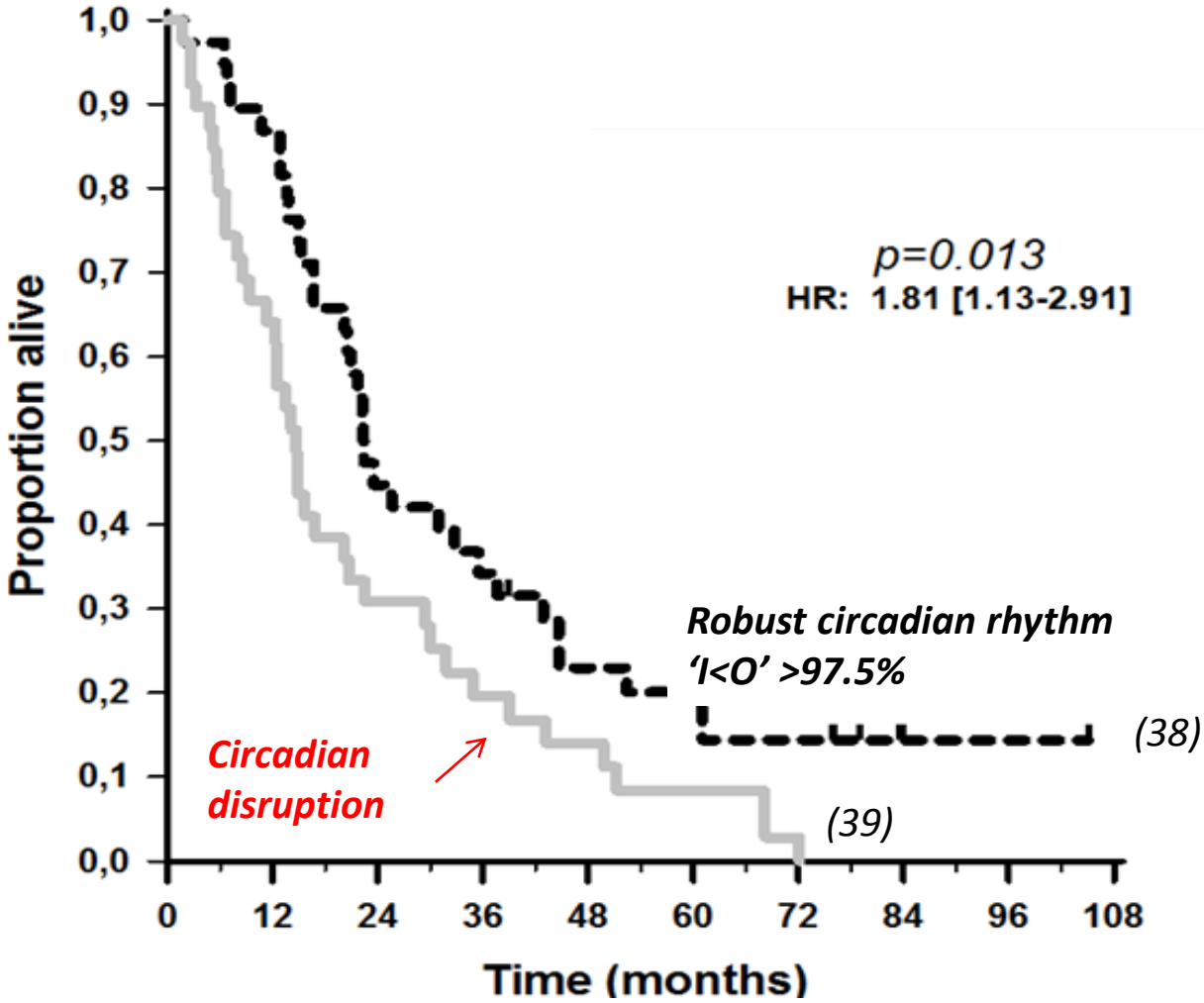


PS = 4

Asthenia grade 3

Anorexia, grade 3

Circadian disruption of rest-activity in patients on chemotherapy a significant predictor of poor survival



77 patients with metastatic colorectal cancer

Innominato et al. Int J Cancer 2012

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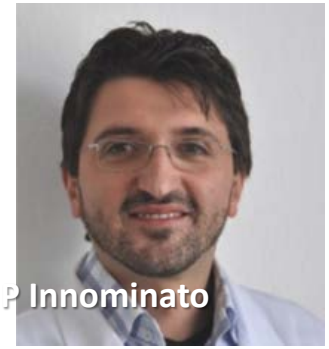
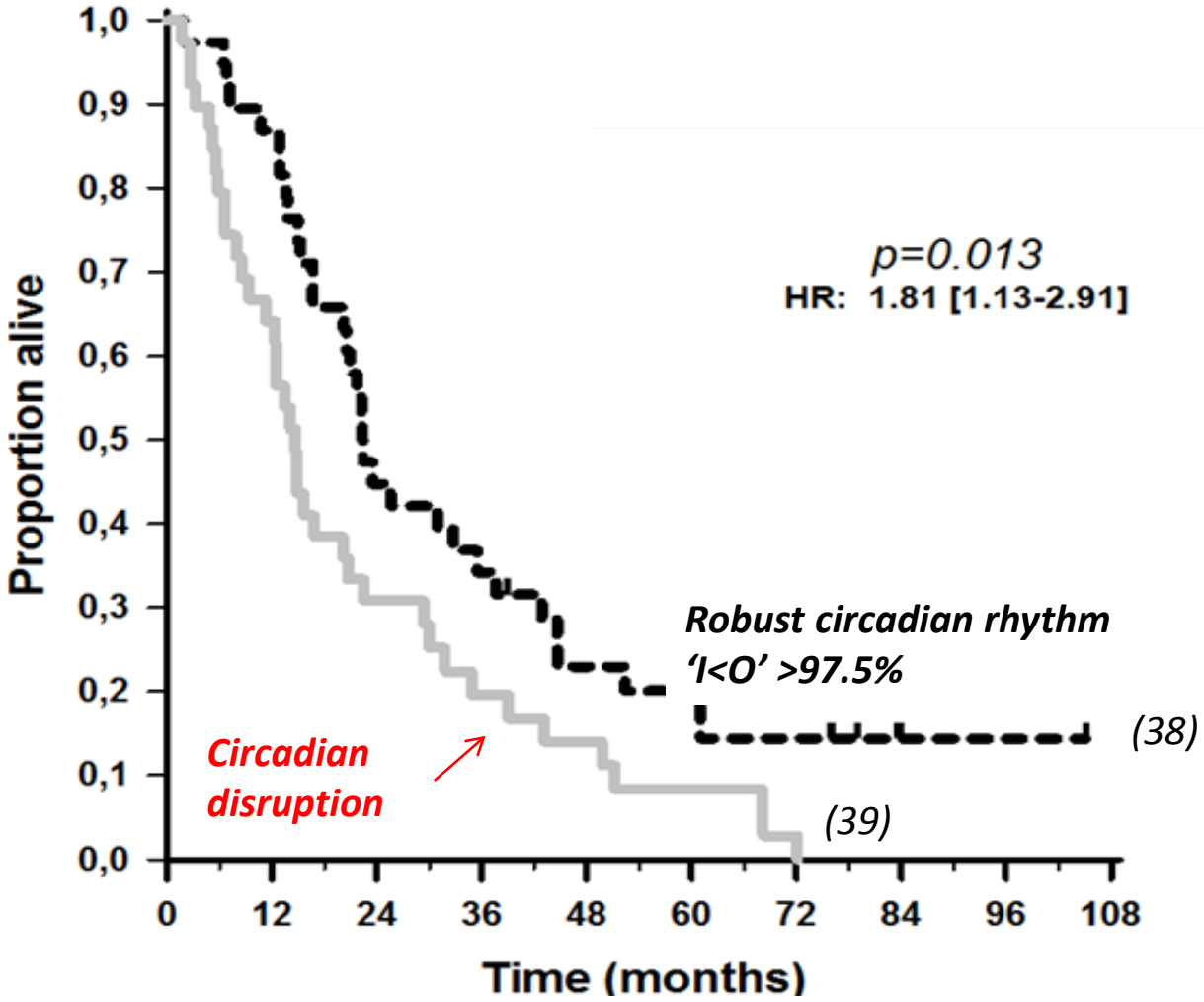




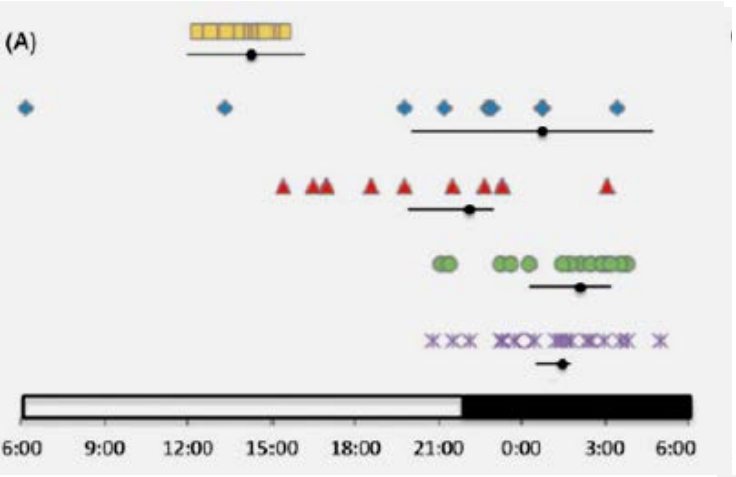
77 patients with metastatic colorectal cancer

Innominato et al. Int J Cancer 2012

Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms

10 individual patients before, during and after a 4-day course of chronotherapy

Before



Time (clock hours)

Rest-activity ***Temperature patch*** ***#1*** ***#2*** ***#3*** ***#4***

Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms

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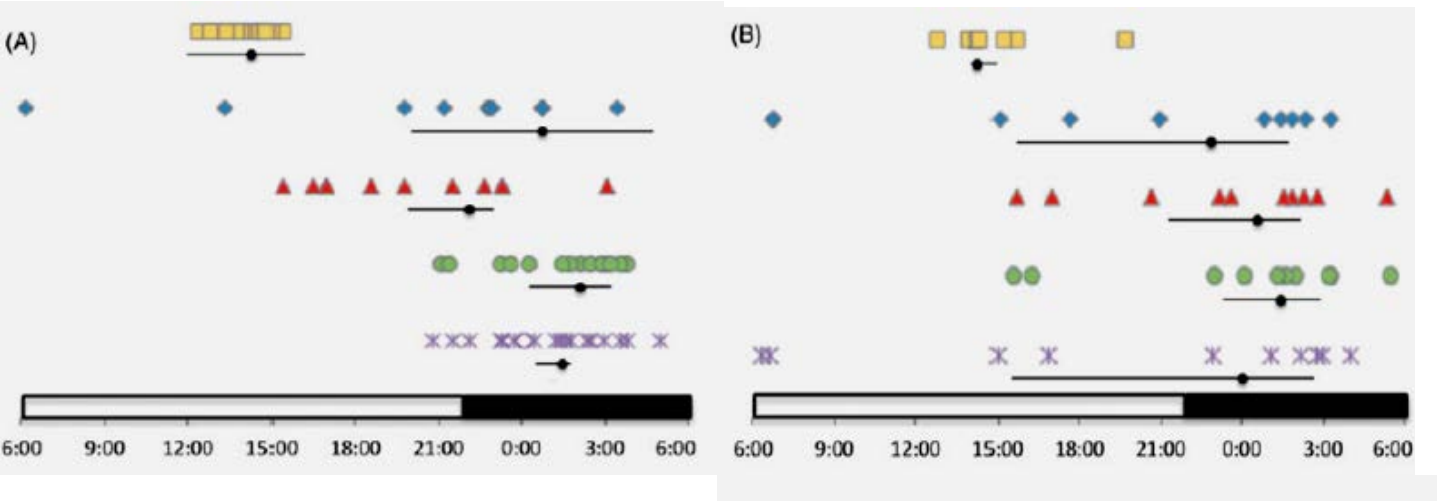
Before ***During***



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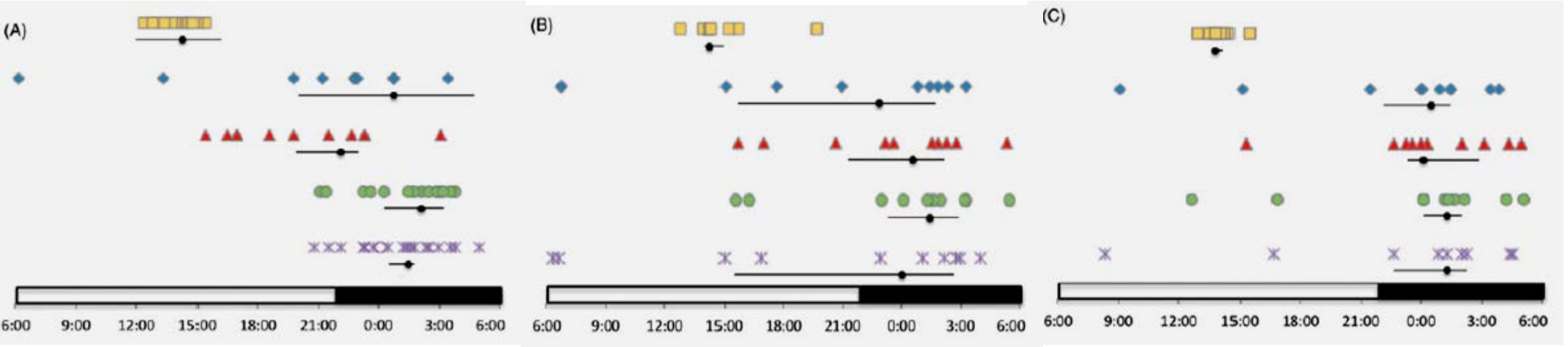
Before ***During*** ***After***



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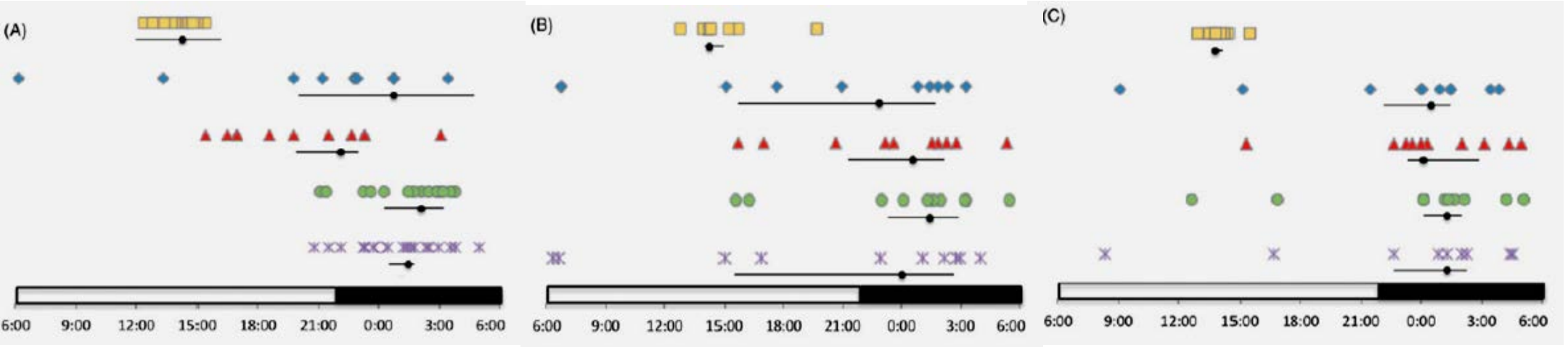

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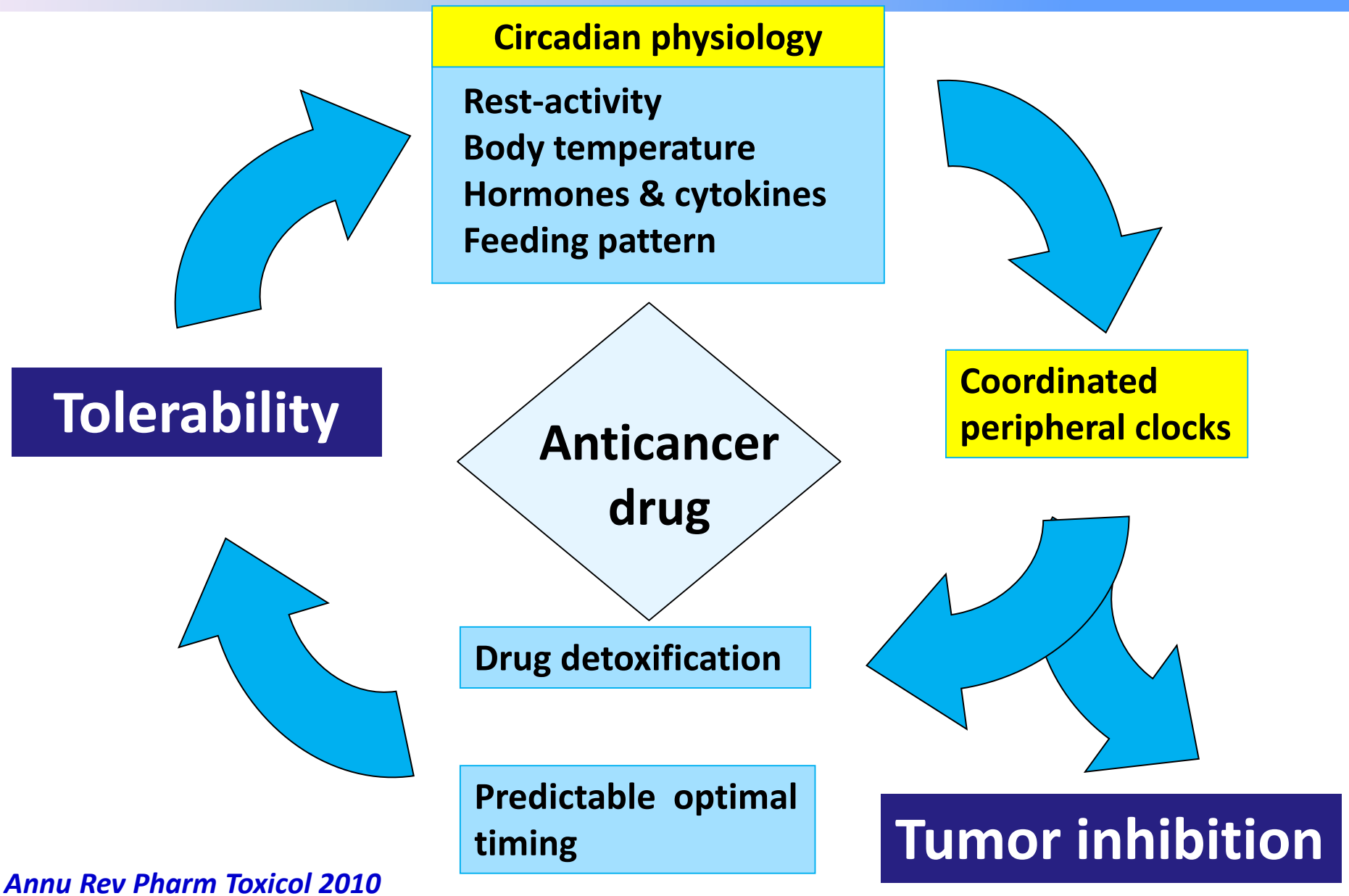
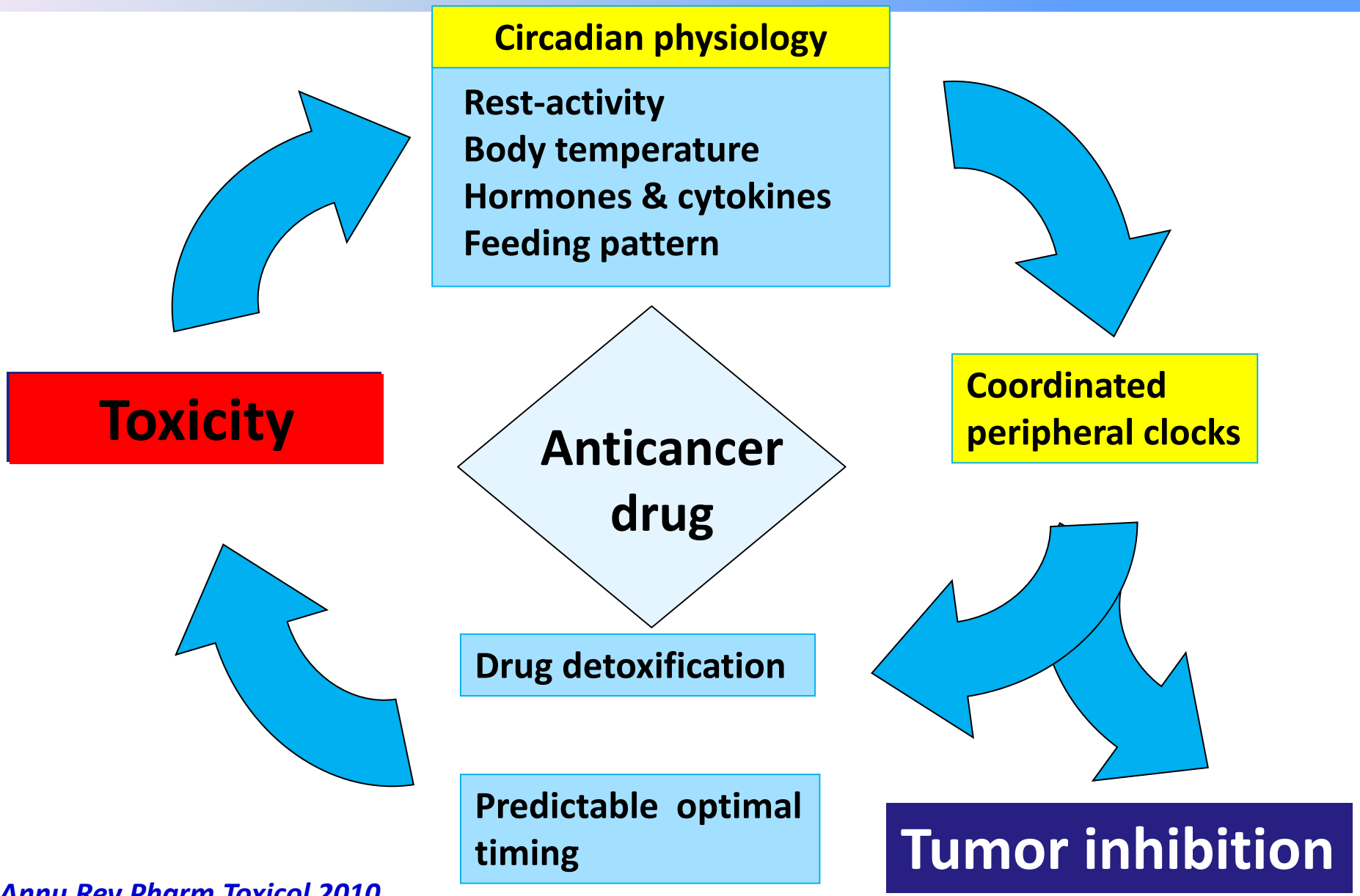
Systems Cancer Chronotherapeutics



Lévi et al. Annu Rev Pharm Toxicol 2010

Systems Cancer Chronotherapeutics



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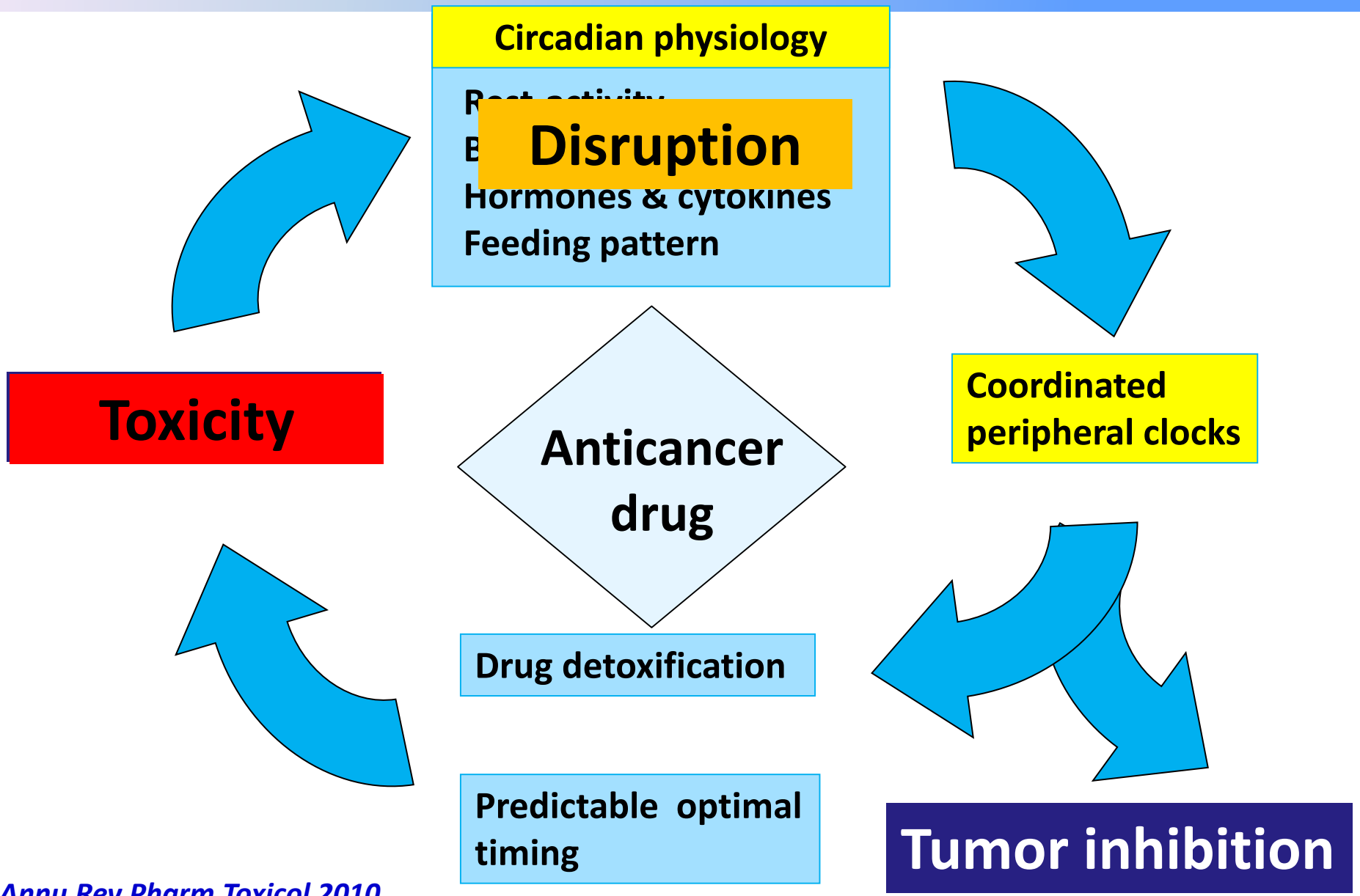

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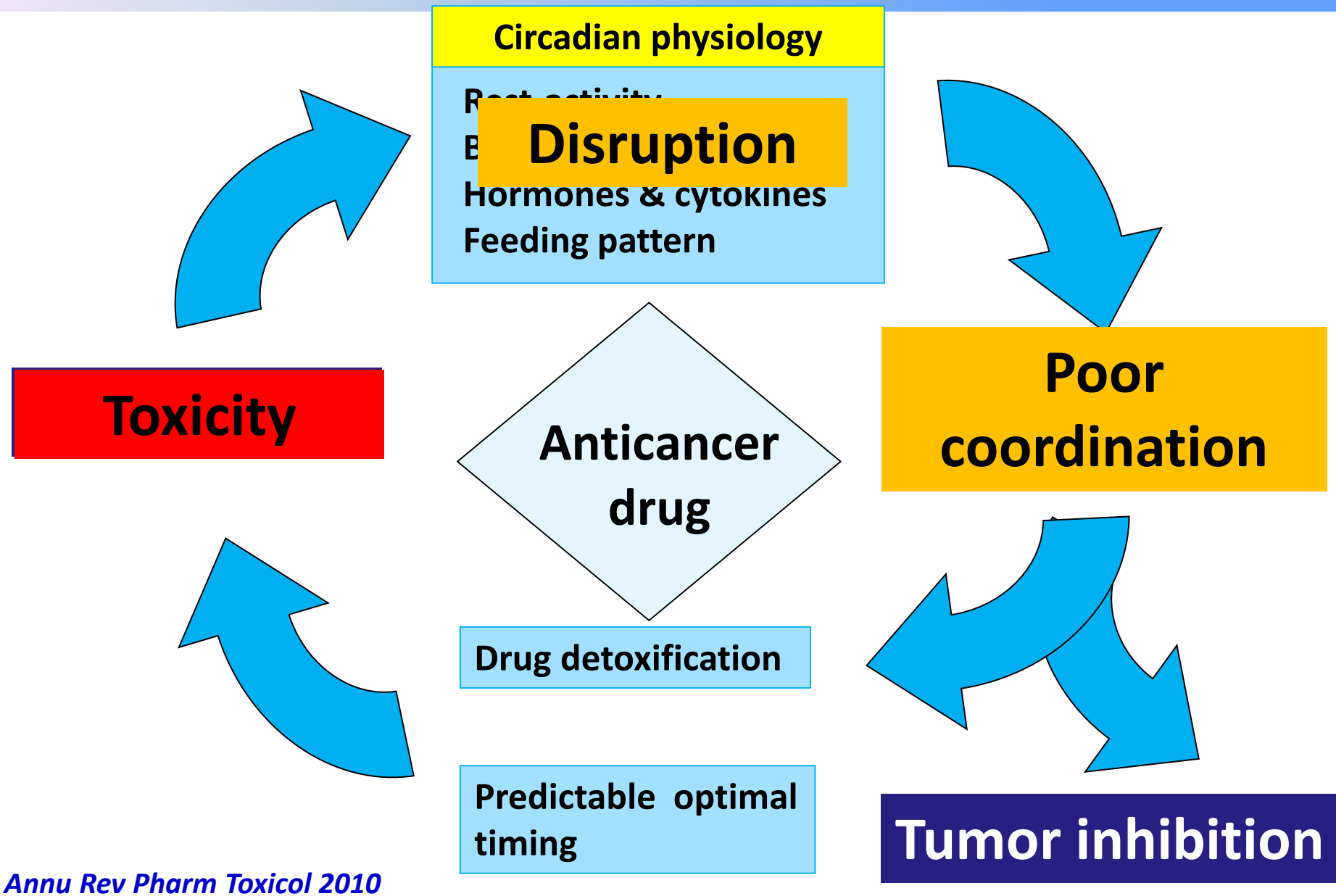

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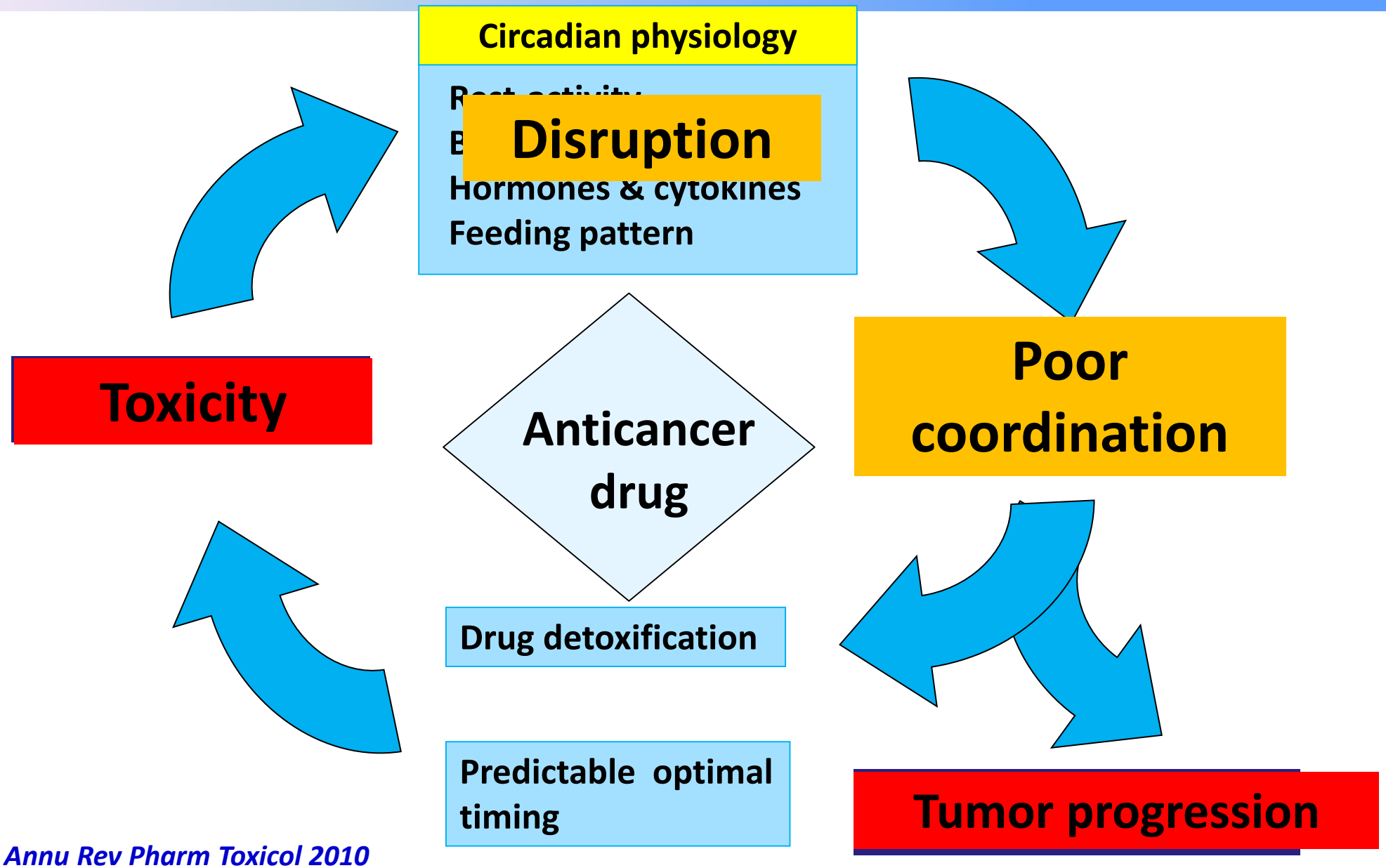

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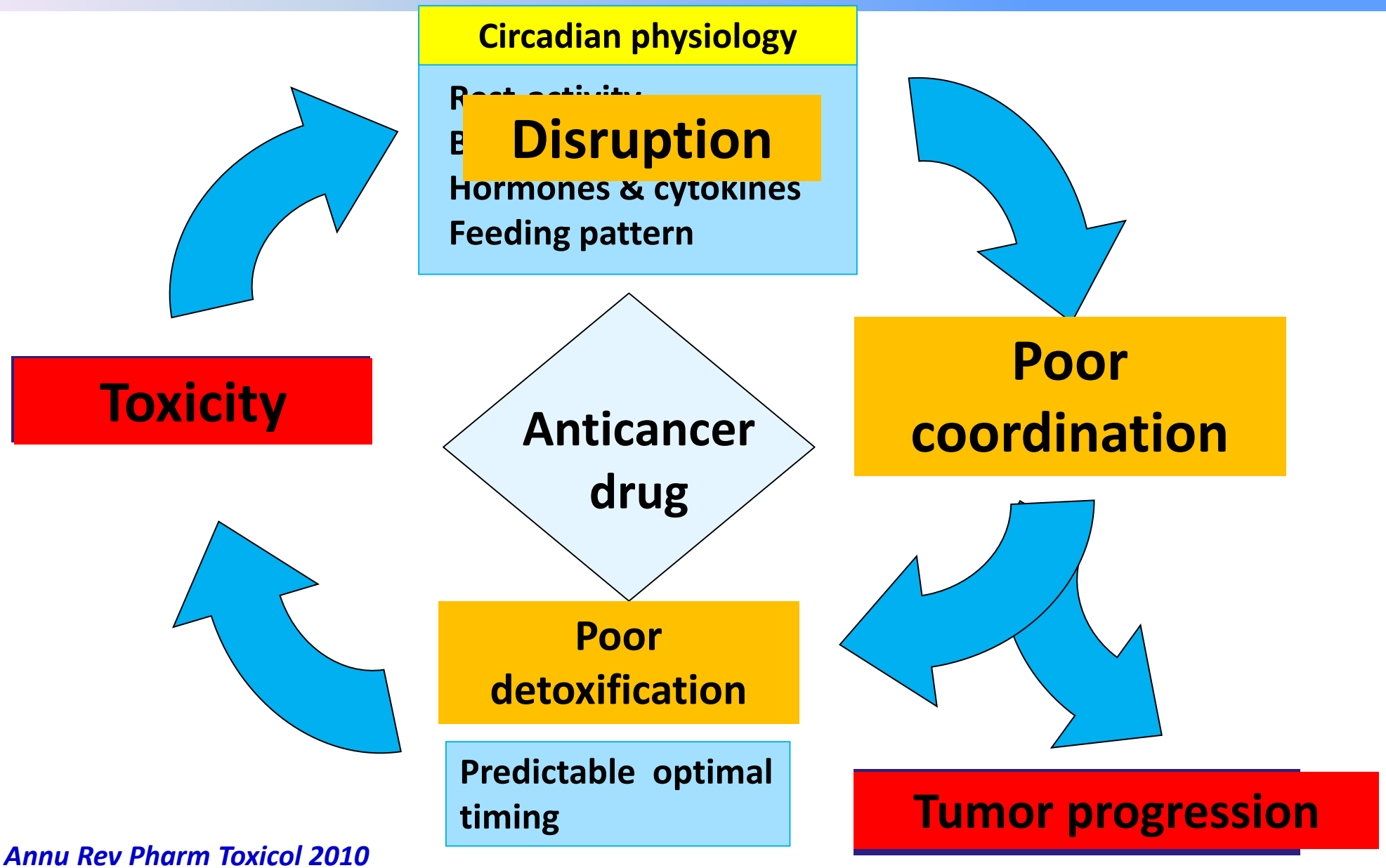
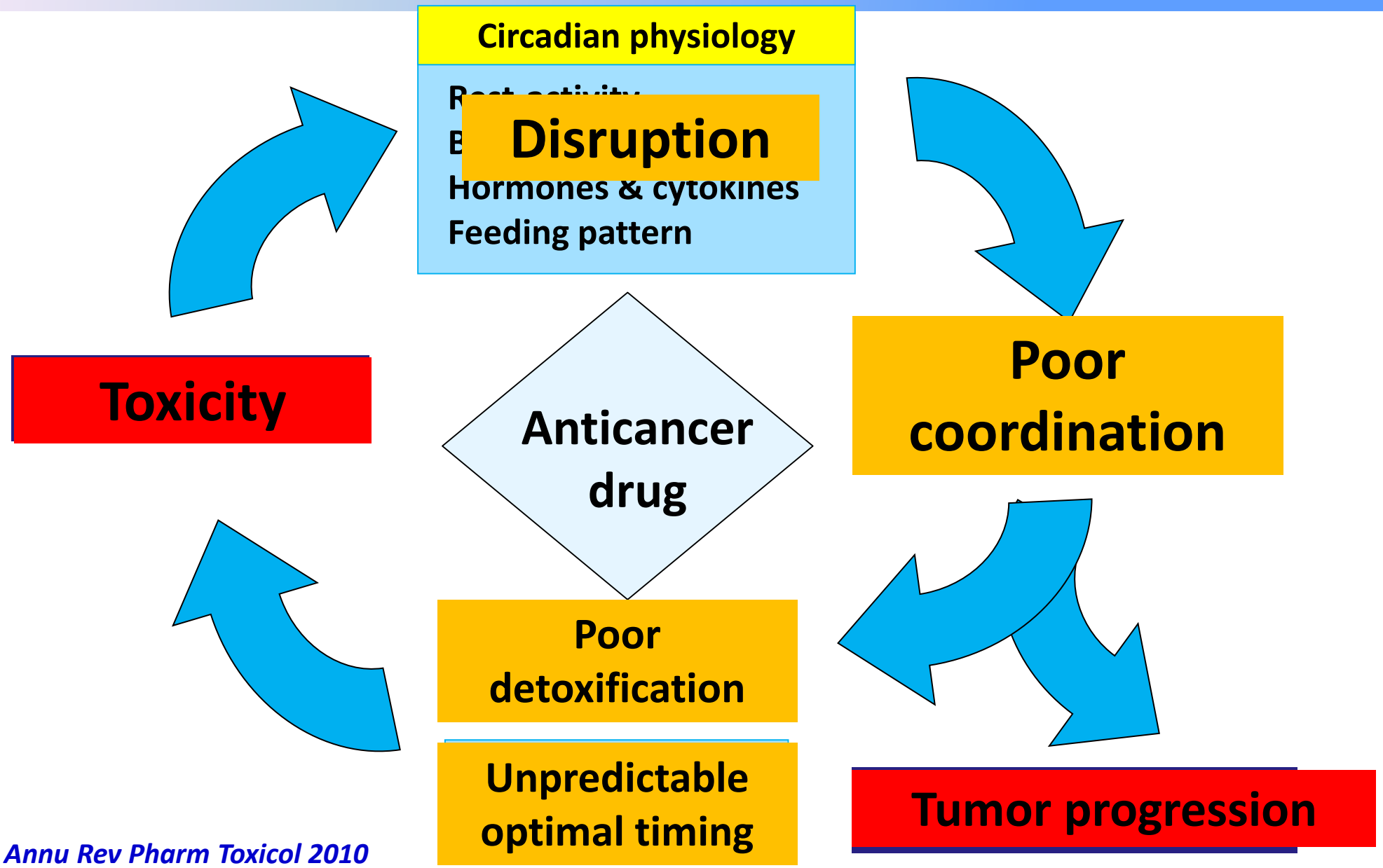


Lévi et al. Annu Rev Pharm Toxicol 2010

Systems Cancer Chronotherapeutics



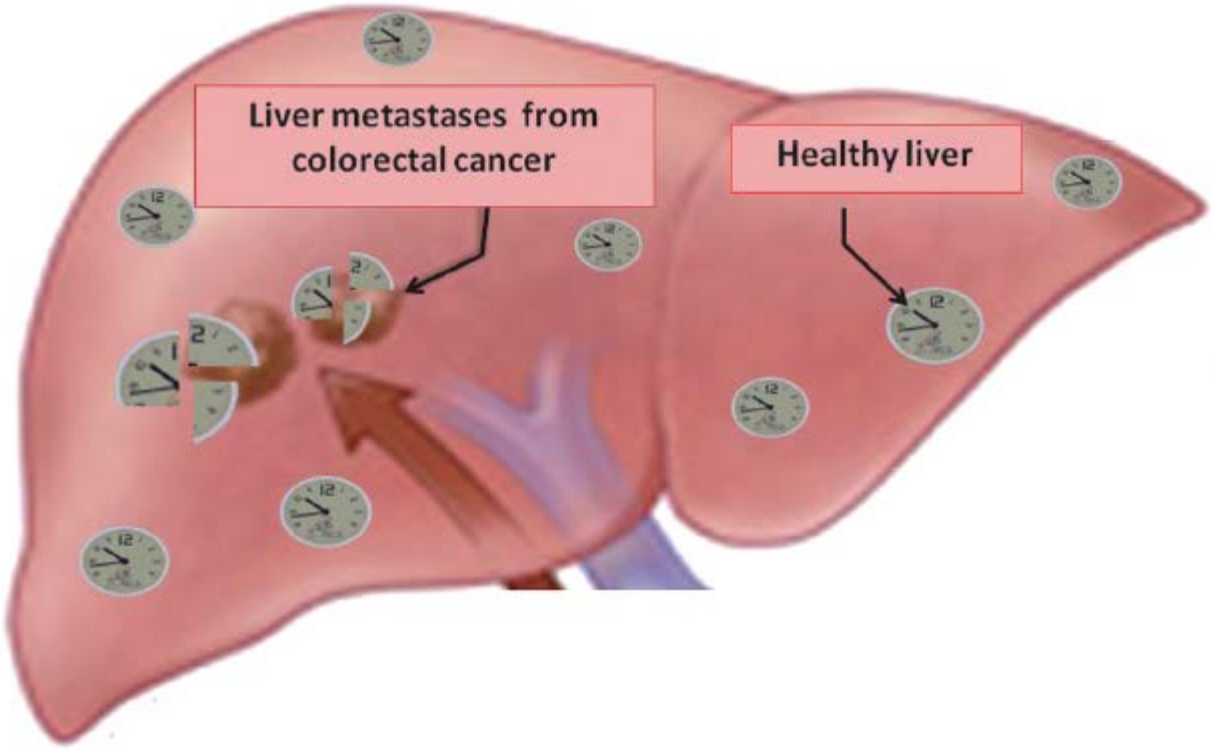
Lévi et al. Annu Rev Pharm Toxicol 2010

A shift in paradigm of cancer treatments?

Conventional chemotherapy principle:
The more the toxicity, the better the efficacy

Chronotherapeutics principle:
The better the tolerability, the better the efficacy!

Circadian clocks in healthy liver cells
Disrupted clocks in cancer cells



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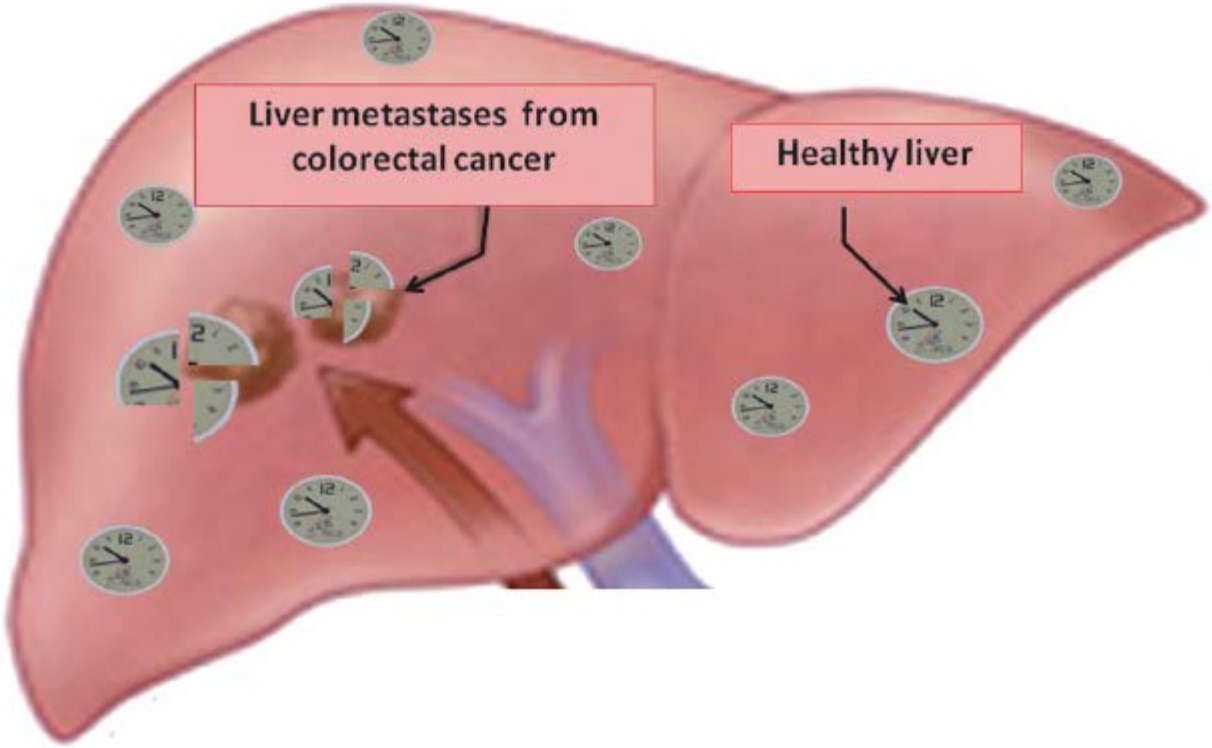

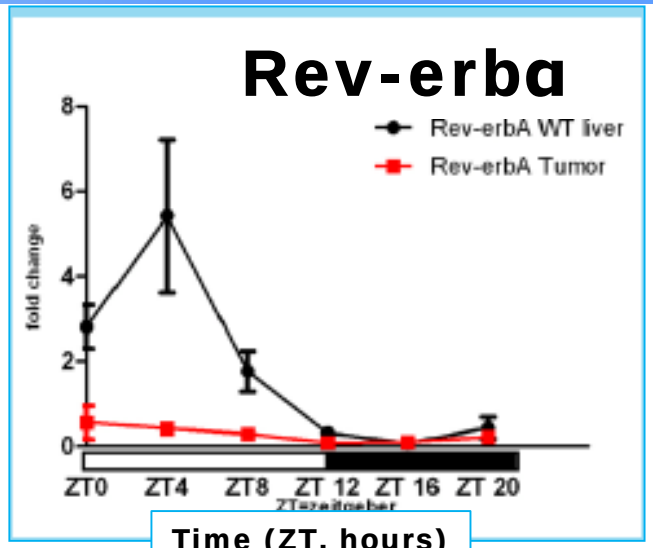

***Huisman et al. Cancer Res* 2011**
71 (8, Suppl 1), abstr 1515

Systems Cancer Chronotherapeutics

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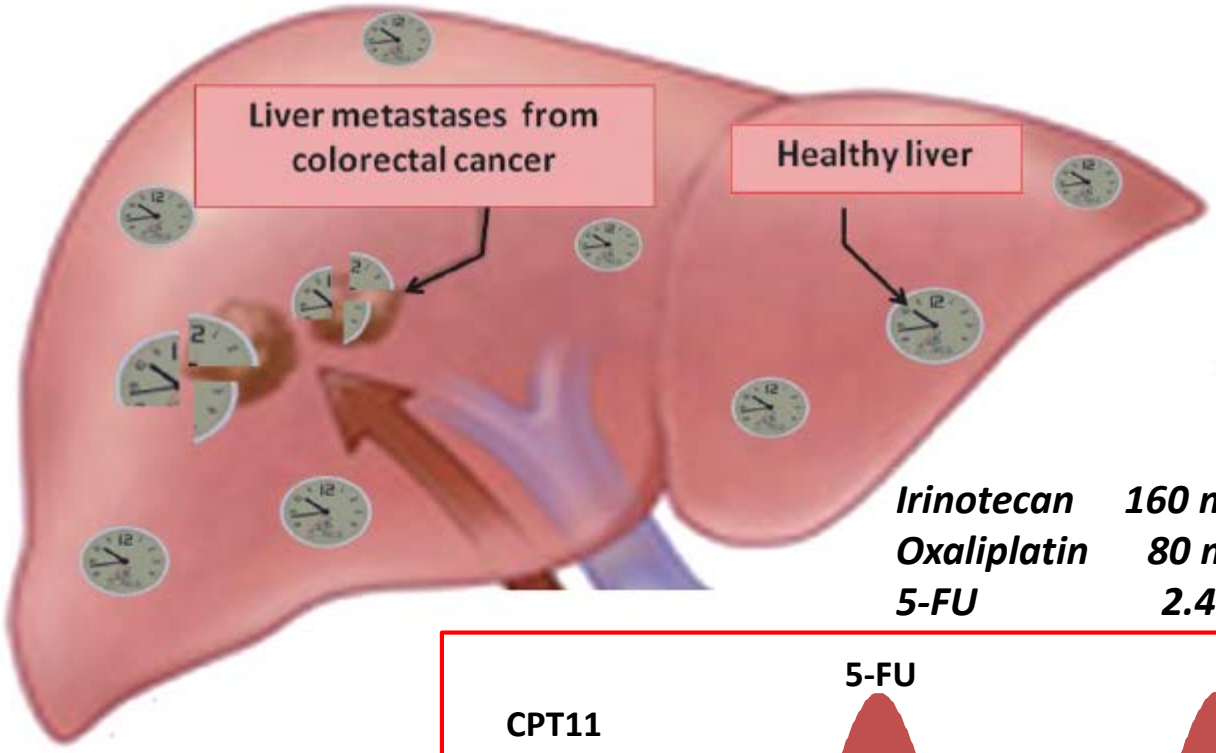
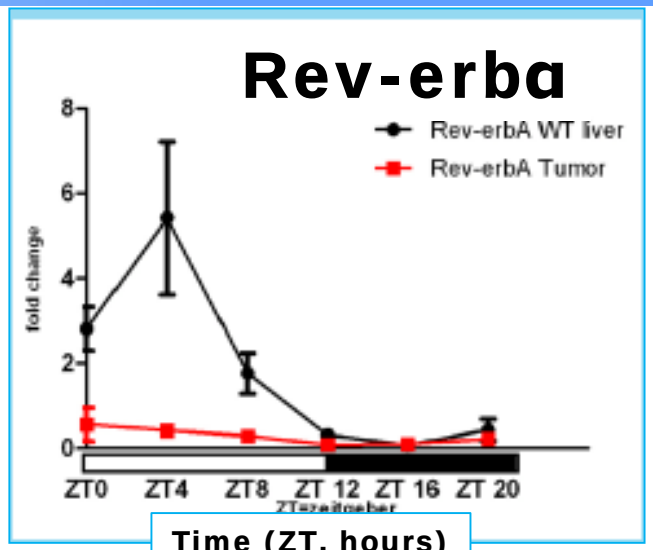
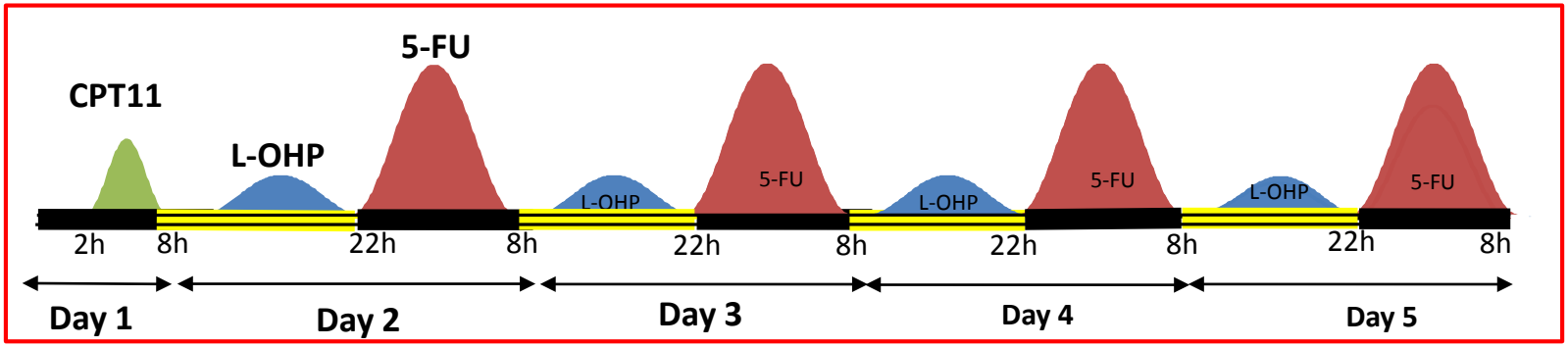




Huisman et al. Cancer Res 2011
71 (8, Suppl 1), abstr 1515

Irinotecan	*160 mg/m² day1*
Oxaliplatin	*80 mg/m² days2-5*
5-FU	*2.4 g/m² days 2-5*

Every 3 weeks



Bouchahda et al. Cancer 2009

- Clock- Cell cycle coupling at single cell level
- Clock- Chronopharmacology at cell population level
- Cancer Chronopharmacology in mice
- Cancer Chronotherapy in patients

Integration into home care

Systems Cancer Chronotherapeutics

inCASA

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

GP

Systems Cancer Chronotherapeutics

inCASA

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GP

Home Gateway

Tele-health System (SARA)

GPRS or IP Network

Actimetry

Tele-health

Remote Service Provider

Hydra Middleware

Tele-health Service (SARA)

Technical Provider

Medical Response

Medical Web App

Contact Centre

Social Response

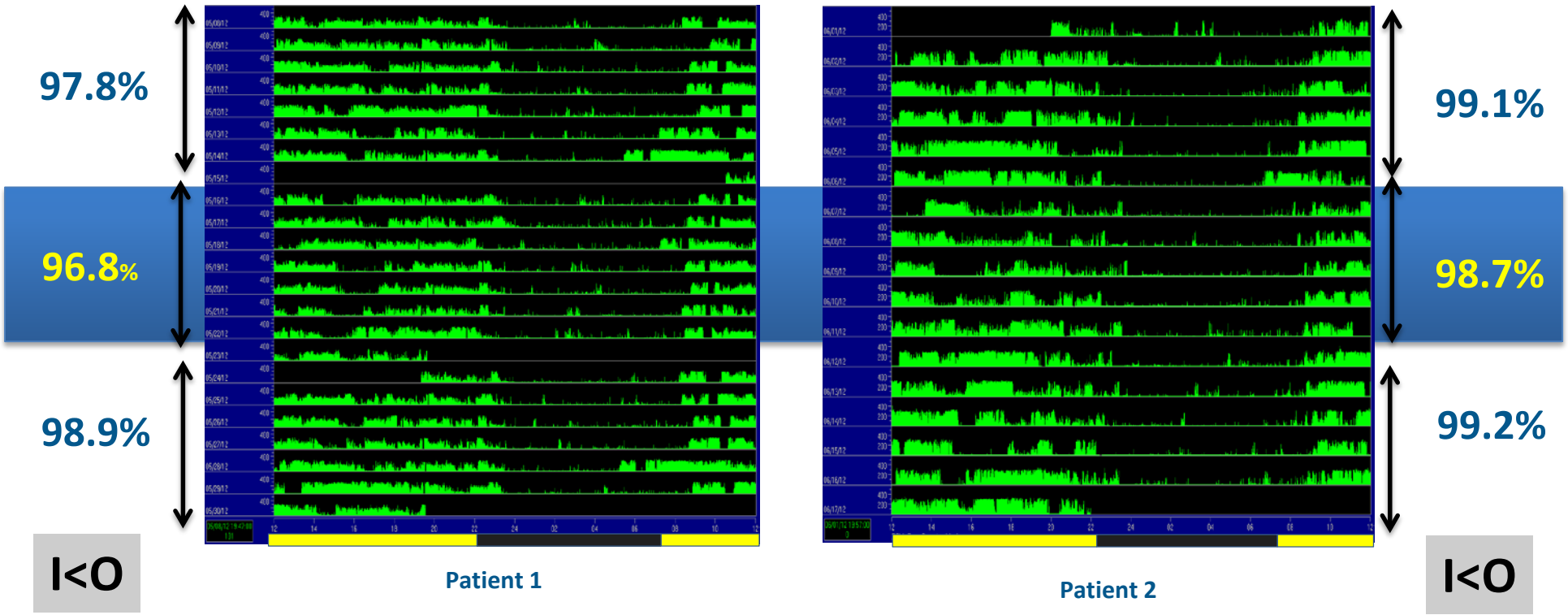
MEDICAL l'esprit de service

Body weight

Self-rated symptoms (MDASI)

Rest-activity rhythm

Daily teletransmission of rest-activity pattern throughout chronotherapy (chronoIFLO4) at home



Two patients with mCRC or pancreatic ca on Irinotecan, Oxaliplatine, 5-Fluorouracile, Leucovorin (chronoIFLO4)

Objectives

Patient-centered health system integrating biological rhythms, information & communication technologies, services, and patient chart

For improving patient autonomy, QoL, & survival through medical progress stimulation

- Early non invasive **detection of predictors of health alteration in chronic disease patients (cancer)**
- Proactive interventions for preventing patient deterioration and emergency hospitalization
- **Adjustment of treatment delivery to the individual patient and to his (her) own clocks**

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Altran, Voluntis, FSI, Axon Cable, Blue Linea, UTT, Univ Reims, INSERM

Objectives

Patient-centered health system integrating biological rhythms, information & communication technologies, services, and patient chart

For improving patient autonomy, QoL, & survival through medical progress stimulation

- Early non invasive **detection of predictors of health alteration in chronic disease patients (cancer)**
- Proactive interventions for preventing patient deterioration and emergency hospitalization
- **Adjustment of treatment delivery to the individual patient and to his (her) own clocks**

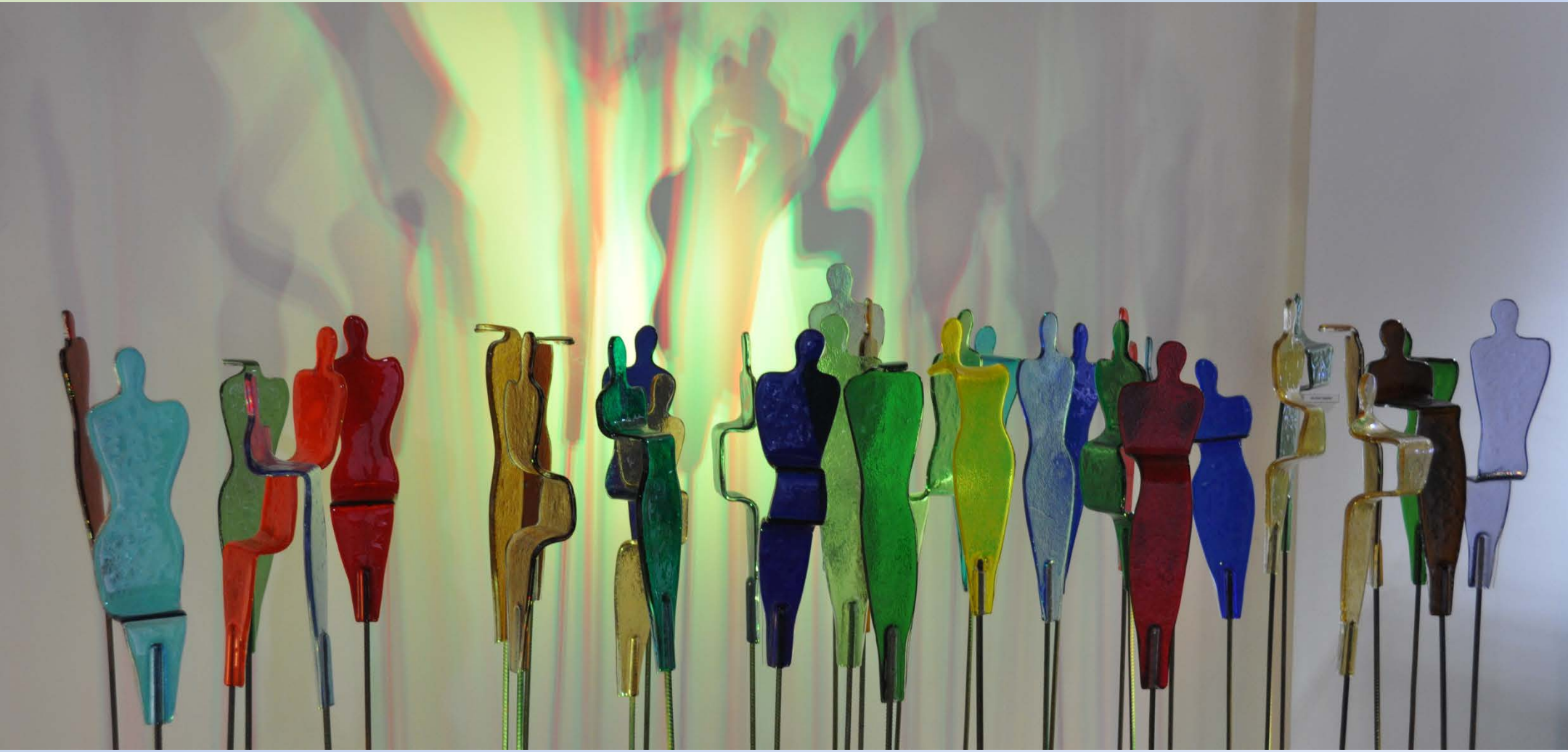
Altran, Voluntis, FSI, Axon Cable, Blue Linea, UTT, Univ Reims, INSERM

IJGodinot, AP-HP, LVL médical, CEA, MADOPA, Thuasne Médical

Conclusions

- Circadian clocks control cancer processes and treatment effects
- Targeting host and/or tumor clocks could improve patient outcomes
- Joint optimization of tolerability & efficacy in each patient through personalized chronotherapy delivery according to CTS monitoring at home
- Mathematical models and dedicated technologies for designing optimal treatment strategy & delivering optimal chronotherapy schedule

Systems Cancer Chronotherapeutics



Systems Cancer Chronotherapeutics

Rythmes Biologiques et Cancers

Cancersensor
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